PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re United States Patent No. 4,598,089

Attn: Box Patent Ext.

Inventors: Hadvary et al.

Issue Date: July 1, 1986

For: Leucine Derivatives

APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. § 156

Nutley, New Jersey 07110
May 20, 1999

Assistant Commissioner for Patents
Washington, D.C. 20231

S i r:

Pursuant to 35 U.S.C. § 156, HLR Technology Corporation ("HLR"), a wholly owned subsidiary of Hoffmann-La Roche Inc., which is incorporated under the laws of the State of New Jersey, and owns U.S. Patent No. 4,598,089 by virtue of an assignment executed on May 1, 1999 and submitted for recordation by the United States Patent and Trademark Office on May 3, 1999, submits this Application for extension of its term.[1]

[1] Assignments from the inventors to F.Hoffmann-La Roche & Co., Aktiengesellschaft and from F.Hoffmann-La Roche & Co., Aktiengesellschaft to Hoffmann-La Roche Inc. ("Roche"), a corporation organized under the laws of the State of New Jersey, were recorded on October 9, 1984, at reel 4308, frames 453-456.

U.S. Patent No. 4,589,089
Issue Date: July 1, 1986

Applicant seeks extension of the term of U.S. Patent No. 4,598,089 for five (5) years from June 18, 2004 to June 18, 2009 and certification that it is entitled to the rights derived from this patent as set forth in 35 U.S.C. § 156(b).

The information contained in this document and its Exhibits is provided in accordance with 35 U.S.C. § 156(d) and 37 C.F.R. § 1.740 and is listed in the manner set forth in § 1.740.

(1) A Complete Identification Of The Approved Product As By Appropriate Chemical And Generic Name, Physical Structure Or Characteristics

The approved product contains orlistat as the sole active ingredient in the drug Xenical® (a copy of the approved physician package insert is attached as Exhibit 1).

"Orlistat" is the non-proprietary name approved by the USAN counsel for the active ingredient in Xenical®.

Orlistat also has the following chemical names:

1. (2S,3S,5S)-5-[(S)-2-formamido-4-methyl-valeryloxy]-2-hexyl-3-hydroxy-hexadecanoic 1,3 acid lactone; and

(S)-2-formylamino-4-methyl-pentanoic acid (S)-1-[(2S,3S)-3-hexyl-4-oxo-2-oxetanyl]methyl]-dodecyl ester; and

[2S-[2α(R*),3β]]-N-formyl-L-leucine 1-[(3-hexyl-4-oxo-2-oxetanyl)methyl] dodecyl ester; and

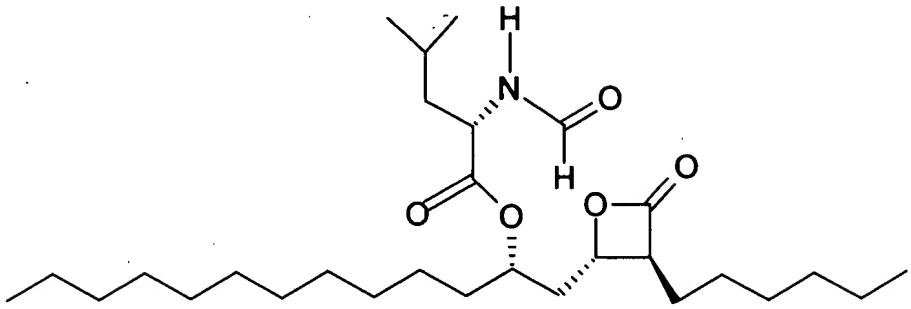
N-formyl-L-leucine ester with (3S,4S)-3-hexyl-4-[(2S)-2-hydroxytridecyl]-2-oxetanone; and

orlipastat; and

Ro 18-0647; and

Tetrahydrolipstatin.

2. Orlistat has the structural formula:



The term "approved product" is defined in 35 U.S.C. § 156(a) as the "product" referred to in paragraphs (4) and (5) of subsection (a). In turn, the word "product" is defined in 35 U.S.C. § 156(f)(1)(A) to comprise a "drug product" which is described in 35 U.S.C. § 156(f) (2) to include "the active ingredient of a new drug, antibiotic drug, or human biological product . . . as a single entity or in combination with another active ingredient." Accordingly, the approved product subject to this Application includes orlistat as a single ingredient or in combination with another active ingredient.

(2) A Complete Identification Of The Federal Statute Including The Applicable Provision Of Law Under Which The Regulatory Review Occurred

The regulatory review occurred under Section 505 of the Federal Food, Drug and Cosmetic Act ("FD&C Act"), 21 U.S.C. § 301 *et seq.*

(3) An Identification Of The Date On Which The Product Received Permission For Commercial Marketing Or Use Under The Provision Of Law Under Which The Applicable Regulatory Review Period Occurred

The Food and Drug Administration ("FDA") approved orlistat (Xenical®) for commercial marketing or use under Section 505 of the FD&C Act on April 23, 1999 (Exhibit 2).

(4) In The Case Of A Drug Product, An Identification Of Each Active Ingredient In The Product And As To Each Active Ingredient, A Statement That It Has Not Been Previously Approved For Commercial Marketing Or Use Under The Federal Food, Drug, And Cosmetic Act, The Public Health Service Act, Or The Virus-Serum-Toxin Act, Or A Statement Of When The Active Ingredient Was Approved For Commercial Marketing Or Use (Either Alone Or In Combination With Other Active Ingredients), The Use For Which It Was Approved, And The Provision Of Law Under Which It Was Approved

The sole active ingredient in the approved product is orlistat, which active ingredient has not been previously approved for commercial marketing or use under the FD&C Act, The Public Health Services Act or the Virus-Serum-Toxin Act.

(5) A Statement That The Application Is Being Submitted Within The Sixty Day Period Permitted For Submission Pursuant to § 1.720(f) And An Identification Of The Date Of The Last Day On Which The Application Could Be Submitted

This application is being submitted within the permitted sixty (60) day period, the last day of which is June 22, 1999.

(6) A Complete Identification Of The Patent For Which An Extension Is Being Sought By The Name Of the Inventor, The Patent Number, The Date Of Issue, And The Date of Expiration

The complete identification of the patent for which an extension is being sought is:

Inventors:	Paul Hadvary Erich Houchuli Ernst Kupfer Hans Lengsfeld Ernst K. Weibel
Patent No:	4,598,089
Issue Date:	July 1, 1986
Expiration Date:	June 18, 2004 (without extension)

(7) A Copy Of The Patent For Which An Extension Is Being Sought, Including The Entire Specification (Including Claims) And Drawings

A copy of U.S. Patent No. 4,598,089 is attached as Exhibit 3.

(8) A Copy Of Any Disclaimer, Certificate Of Correction, Receipt Of Maintenance Fee Payment, Or Reexamination Certificate Issued In the Patent

No disclaimer, certificate of correction, or reexamination certificate has been issued for U.S. Patent No. 4,598,089. Copies of the receipts for maintenance fee payments are attached as Exhibit 4.

(9) A Statement That The Patent Claims The Approved Product Or A Method Of Using Or Manufacturing The Approved Product, And A Showing Which Lists Each Applicable Patent Claim And Demonstrates The Manner In Which Each Applicable Patent Claim Reads On The Approved Product Or Method Of Using Or Manufacturing The Approved Product

United States Patent No. 4,598,089 claims the approved product, orlistat, in claims 1, 3, 4, 5, 6, and 8, claims methods of using the approved product, orlistat, in claims 9, 11, 12, 13, 15, 16, 17, 19, and 20.[2]

Claims 1 and 3 are compound claims that claim orlistat, the active ingredient in Xenical®. Claim 1 specifically claims the compound orlistat when "A" in the formula is $-(CH_2)_5-$. Claim 3

[2] Certain of the claimed methods of using the approved product may not relate to a presently FDA-approved method of using the approved product. Xenical® is indicated for obesity management including weight loss and weight maintenance when used in connection with a reduced-calorie diet. Xenical® is also indicated to reduce the risk for weight regain after prior weight loss. Xenical® is indicated for obese patients with an initial body mass index (BMI) $\geq$ 30 kg/m^2 or $\geq$ 27 kg/m^2 in the presence of other risk factors (e.g., hypertension, diabetes, dyslipidemia). FDA presently approves no other use.

claims the compound orlistat *per se* as (2S,3S,5S)-5-[(S)-2-formamido-4-methyl-valeryloxy]-2-hexyl-3-hydroxy-hexadecanoic 1,3 acid lactone. Therefore, claims 1 and 3 read on the approved product.

Claims 4, 5, 6, and 8 are pharmaceutical composition claims. Claim 4 claims a pharmaceutical composition comprising (a) about 5% to about 95% of orlistat (when "A" in the formula is $-(CH_2)_5-$) and (b) 5% to 95% of a pharmaceutically acceptable inert carrier material. The claimed composition is in unit dosage form and present in an amount sufficient to supply about 0.1 to about 100 mg of orlistat (when "A" in the formula is $-(CH_2)_5-$) per kilogram of body weight of the patient per day.

Each capsule of Xenical® contains approximately fifty percent (50%) by weight of orlistat and fifty percent (50%) by weight of inert carrier material in unit dosage form.[3] This amount of orlistat falls within the 5% to 95% ranges found in claim 4. The dosing schedule for Xenical®, as set forth in Exhibit 1, is 120 mg three times per day for a total of 360 mg. Most humans have a mass between 25 kg and 250 kg. Using this broad range of body weights, claim 4 claims a pharmaceutical composition that provides between 25 mg and 2,500 mg of orlistat per day. Three hundred sixty (360) mg is within this range. Accordingly, Xenical® is encompassed by claim 4, which claim reads on the approved product.

Claim 5 adds the requirement to claim 4 that the composition must be in oral unit dosage form. Xenical® is formulated in oral unit dosage form and thus is encompassed by claim 5. Claim

[3] The capsules contain 120 mg of the active ingredient, orlistat and, on information and belief, approximately 120 mg of the inactive ingredients microcrystalline cellulose, sodium starch glycolate, sodium lauryl sulfate, povidone, and talc.

6 further requires that the oral dosage form be formulated as a tablet, dragee, capsule, solution, emulsion or suspension. Xenical® is formulated as a capsule and thus is encompassed by claim 6. Claim 8 requires that the compound be (2S,3S,5S)-5-[(S)-2-formamido-4-methyl-valeryloxy]-2-hexyl-3-hydroxy-hexadecanoic 1,3 acid lactone, which is orlistat *per se*. Accordingly, claims 5, 6 and 8 read on the approved product.

Claims 9, 11, and 12 are directed to a method of treating obesity.[4] Claim 9 claims a method of treating obesity in an afflicted mammal comprising administering to the mammal orlistat (when "A" in the formula is $-(CH_2)_5-$) in an amount effective in treating obesity and thus reads on a method of using the approved product. Claim 11 further requires that the compound be (2S,3S,5S)-5-[(S)-2-formamido-4-methyl-valeryloxy]-2-hexyl-3-hydroxy-hexadecanoic 1,3 acid lactone, which is orlistat *per se*. Accordingly, claim 11 reads on a method of using the approved product. Claim 12 additionally requires that the orlistat (when "A" in the formula is $-(CH_2)_5-$) be administered in a daily dose of from about 0.1 mg to 100 mg/kg body weight of the mammal. This range is identical to that discussed above for the pharmaceutical composition of claim 4 and therefore reads upon a method of using Xenical®. Thus, claims 9, 11, and 12 read on a method of using the approved product.

Claims 13, 15, and 16 are directed to a method of treating hyperlipaemia.[5] Claim 13 claims a method of treating hyperlipaemia in an afflicted mammal comprising administering to the

[4] Claims 9, 11, and 12 are directed to a presently FDA-approved method, i.e. obesity management.

[5] Claims 13, 15, and 16 are directed to a method that is not presently approved by FDA, i.e. treating hyperlipaemia. While 35 U.S.C. § 156(b) states "the rights derived from any patent the term of which is extended under this section shall during the period during which the term of the patent is extended .... in the case of a patent which claims a method of using a product, be

mammal orlistat (when "A" in the formula is $-(CH_2)_5-$) in an amount effective in treating hyperlipaemia and thus reads on a method of using the approved product. Claim 15 further requires that the compound be (2S,3S,5S)-5-[(S)-2-formamido-4-methyl-valeryloxy]-2-hexyl-3-hydroxy-hexadecanoic 1,3 acid lactone, which is orlistat *per se*. Accordingly, claim 15 reads on a method of using the approved product. Claim 16 additionally requires that the orlistat (when "A" in the formula is $-(CH_2)_5-$) be administered in a daily dose of from about 0.1 mg to 100 mg/kg body weight of the mammal. This range is identical to that discussed above for the pharmaceutical composition of claim 4 and therefore reads on a method of using Xenical®. Thus, claims 13, 15 and 16 read on a method of using the approved product.

Claims 17, 19, and 20 are directed to a method of preventing obesity. [6] Claim 17 claims a method of preventing obesity in a mammal comprising administering to the mammal orlistat (when "A" in the formula is $-(CH_2)_5-$) in an amount effective in preventing obesity by inhibiting pancrease lipase and thus reads on a method of using the approved product. Claim 19 further requires that the compound be (2S,3S,5S)-5-[(S)-2-formamido-4-methyl-valeryloxy]-2-hexyl-3-hydroxy-hexadecanoic 1,3 acid lactone, which is orlistat *per se*. Accordingly, claim 19 reads on a method of using the approved product. Claim 20 additionally requires that the orlistat (when "A" is $-(CH_2)_5-$) be administered in a daily dose of from about 0.1 mg to 100 mg/kg body weight of the mammal. This range is identical to that discussed above for the pharmaceutical composition of claim 4 and

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limited to any use claimed by the patent and approved for the product," 37 C.F.R. § 1.740(a)(9) requires "a showing which lists each applicable patent claim and demonstrates the manner in which each applicable patent claim reads on the approved product or method of using or manufacturing the approved product." Claims 13, 15, and 19 are addressed in view of the C.F.R. provision.

[6] Claims 17, 19, and 20 are directed to a presently FDA-approved method, i.e. to reduce the risk for weight regain after prior weight loss.

therefore reads on a method of using Xenical®. Thus, claims 17, 19 and 20 read on a method for using the approved product.

(10) A Statement, Beginning on a New Page, of The Relevant Dates And Information Pursuant To 35 U.S.C. 156(g) In Order To Enable The Secretary Of Health And Human Services Or The Secretary of Agriculture, As Appropriate, To Determine The Applicable Regulatory Review Period As Follows (i): For A Patent Claiming A Human Drug Product, Antibiotic, or Human Biological Product, The Effective Date Of The Investigational New Drug (IND) Application And The IND Number; The Date On Which A New Drug Application (NDA) or a Product License Application (PLA) Was Initially Submitted And The NDA or PLA Number And The Date On which The NDA Was Approved or the Product License Issued

a)	Effective date of the investigational new drug application (IND) and IND number.	June 24, 1988[7] (Exhibit 5) IND No. 31,617
b)	Date on which a New Drug Application (NDA) was initially submitted and NDA number:	November 26, 1996 (Exhibit 6) NDA No. 20-766
c)	Date on which NDA was approved:	April 23, 1999 (Exhibit 2)

[7] Roche's IND No. 31,617 was filed on May 12, 1988 and received by FDA on May 13, 1988. FDA authorized investigations in the IND to begin on June 24, 1988. Applicant believes that the IND should have become effective on June 12, 1988, thirty (30) days after FDA received the IND, and that Applicant should be entitled to rely on this date for the purpose of calculating the term of extension. However, merely to expedite processing, Applicant has used June 24, 1988 as the effective date for all calculations. The use of the June 24, 1988 date is not an admission or waiver of any rights that Applicant may have and is made without prejudice to Applicant amending this Application, if needed.

(11) A Brief Description Beginning On A New Page Of The Significant Activities Undertaken By The Marketing Applicant During The Applicable Regulatory Review Period With Respect To The Approved Product And The Significant Dates Applicable To Such Activities

A chronology of communications involving Roche and the FDA during the regulatory review period is attached as Exhibit 7. This Exhibit 7 lists the date of the communication and a brief summary of the subject matter of the communication. This chronology provides a description of the significant activities undertaken by Roche during the applicable review period. For convenience, the chronology is divided between communications relating to IND No. 31,617 and communications relating to NDA No. 20-766.

If necessary, HLR reserves the right to supplement its summary in Exhibit 7 with materials from which it was derived and other evidence related to Roche's conduct in obtaining the approval of Xenical®, See, e.g., 21 C.F.R. § 60.32.

(12) A Statement Beginning On A New Page That In The Opinion Of The Applicant The Patent Is Eligible For The Extension And A Statement As To The Length Of The Extension Claimed, Including How The Length Of Extension Was Determined

Eligibility

Under the law and in the opinion of Applicant, U.S. Patent No. 4,598,089 is eligible for an extension under 35 U.S.C. § 156.

In particular, 35 U.S.C. § 156(a) in its relevant parts, provide that the term of a patent shall be extended if the following requirements are satisfied: (1) the patent claims a product, a method of using a product or a method of manufacturing a product; (2) the term of the patent has not expired before an application for extension is submitted; (3) the term of the patent has never been extended; (4) an application for extension is submitted by the owner of record of the patent or its agent and in accordance with 35 U.S.C. § 156(d); (5) the product has been subject to a regulatory review period as defined in 35 U.S.C. § 156(a) before its commercial marketing or use; and (6) the permission for the commercial marketing or use of the product after the regulatory review period is the first permitted commercial marketing or use of the product under the provision of law under which such regulatory review period occurred.

These requirements are met as follows:

1. U.S. Patent No. 4,598,089 claims a product and methods of using the product.

2. The term of U.S. Patent No. 4,598,089 presently will expire on June 18, 2004, and thus, the patent has not expired before submission of this Application.

3. The term of U.S. Patent No. 4,598,089 has never been extended under 35 U.S.C. § 156.

4. This Application is submitted by HLR, the owner of record of U.S. Patent No. 4,598,089. This Application is submitted in accordance with 35 U.S.C. § 156(d) and 37 C.F.R. § 1.740 within the sixty (60) day period beginning on April 23, 1999 and ending June 22, 1999. The product received permission for marketing or use under FD&C Act. This Application contains the information required under 35 U.S.C. § 156(d) and 37 C.F.R. § 1.740.

5. The product was subject to a regulatory review period under Sections 505 of the FD&C Act before its commercial marketing or use, as evidenced by the chronology (Exhibit 7) and the Letter of Approval from the FDA, dated April 23, 1999 (Exhibit 2).

6. The permission for the commercial marketing or use of orlistat, after the regulatory review period is the first permitted commercial marketing or use of a product having orlistat in any form as its active ingredient, under the provisions of the FD&C Act under which such regulatory review period occurred. This is confirmed by the absence of any approved drug application for orlistat in any form prior to April 23, 1999.

Accordingly, U.S. Patent No. 4,598,089 satisfies the requirements for an extension under 35 U.S.C. § 156.

Length

In the opinion of Applicant, the term of U.S. patent No. 4,598,089 should be extended for a period of five (5) years, from June 18, 2004 to June 18, 2009.

This extension was determined on the following basis:

Testing Phase (37 C.F.R. § 1.775(c) (1))

For the approved product, that portion of the regulatory review period as defined in 35 U.S.C. 156 (g) (1) (B) (i) ("Testing Phase") commenced on June 24, 1988 and ended on November 26, 1996, which is three thousand seventy-seven (3,077) days.

Application Phase (37 C.F.R. § 1.775(c) (2))

For the approved product, that portion of the regulatory review period as defined under 35 U.S.C. 156 (g) (1) (B) (ii) ("Application Phase") commenced on November 26, 1996 and ended on August 27, 1997, and commenced again on November 14, 1997 and ended on April 23, 1999, which is a total of seven hundred ninety-nine (799) days.[8]

[8] Roche's NDA was withdrawn on August 27, 1997 and was resubmitted on November 14, 1997. HLR maintains that Roche was diligent during the seventy-nine (79) day period in which the NDA was withdrawn as well as all other pertinent time periods. However, since this seventy-nine (79) day period is not needed to obtain the five (5) year maximum extension allowed by law, HLR has not included the mentioned seventy-nine (79) days in the above calculation of the number of days in the Application Phase but reserves the right to do so if later needed.

Regulatory Review Period (37 C.F.R. § 1.775(c))

As defined in 35 U.S.C. 156 (g) (1) (B), the regulatory review period is the sum of the Testing Phase and the Application Phase, which is a total of three thousand eight hundred seventy-six (3,876) days.

Reduction for Review Prior to the Issue of The Patent (37 C.F.R. § 1.775 (d) (1) (i))

The applicable regulatory review period is reduced by that period of review occurring before and on the date the patent issued.

U.S. Patent No. 4,598,089 (Exhibit 3) issued July 1, 1986 and the IND was effective as of June 24, 1988. Accordingly, no reduction for review prior to the issue of the patent applies.

Due Diligence Reduction to Regulatory Review Period (37 C.F.R. § 1.775 (d) (1) (ii))

Under 35 U.S.C. § 156(c) (1), the Testing Phase and Application Phase of the regulatory review period are reduced by the period during which the applicant for the patent extension, in the regulatory review period, did not act with due diligence. In the opinion of the Applicant and illustrated by the summary in Exhibit 7, Roche acted with due diligence during both periods of time. Thus, there is no reduction in the regulatory review period because of lack of due diligence.

One-Half Testing Phase Reduction (37 C.F.R. § 1.775 (d) (1) (iii))

Under 35 U.S.C. § 156(c) (2), the three thousand eight hundred seventy-six (3,876) day regulatory review period is reduced by one-half of the three thousand seventy-seven (3,077) day

Testing Phase. One-half of the Testing Phase is one thousand five hundred thirty-eight and one-half (1,538.5) days. Thus, the three thousand eight hundred seventy-six (3,876) day regulatory review period is reduced by one thousand five hundred thirty-eight and one-half (1,538.5) days leaving a final revised regulatory review period of two thousand three hundred thirty-seven and one-half (2,337.5) days.

Fourteen Year Cap (37 C.F.R. § 1.775 (d) (2) - (4)

Under 35 U.S.C. § 156(c) (3) should the period of time remaining in the term of the patent after the date of approval when added to the period of extension exceed fourteen (14) years, the period of extension is reduced so that the total of both such periods does not exceed fourteen (14) years. In applying section 156(c) (3), the final revised regulatory review period as calculated above two thousand three hundred thirty-seven and one-half (2,337.5) days is added onto the end of the original term of the patent (June 18, 2004) resulting in a date of November 12, 2010.[9] Alternatively, fourteen (14) years is added to the NDA approval date (April 23, 1999) resulting in a date of April 23, 2013. The earlier of the above two dates, November 12, 2010 is selected.

Two and Five Year Extension Limits (37 C.F.R. § 1.775 (d) (5) & (6)

A patent issued after September 24, 1984 is limited to a maximum extension of five years.

U.S. Patent No. 4,598,089 (Exhibit 3) issued on July 1, 1986. Accordingly, the patent is eligible for an extension of up to five years.

[9] The final revised regulatory review period as calculated above two thousand three hundred thirty-seven and one-half (2,337.5) days. Applicant has rounded the half-day in this revised regulatory review period up to the next full day for determining dates.

As set forth above, the term of U.S. Patent No. 4,598,089 is eligible for an extension of five (5) years from June 18, 2004 to June 18, 2009.

(13) A Statement That Applicant Acknowledges A Duty To Disclose To The Commissioner Of Patents And Trademarks And The Secretary Of Health And Human Services Any Information Which Is Material To The Determination Of Entitlement To The Extension Sought

Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to any determinations of entitlement to the extension sought in the Application.

(14) The Prescribed Fee for Receiving and Acting Upon the Application for Extension

Applicant encloses (in duplicate) a transmittal letter requesting the amount of $1120.00 be charged to Account No. 08-2525.

(15) The Name, Address and Telephone Number Of The Person to Whom Inquiries and Correspondence Relating To The Application For Patent Term Extension Are To Be Directed

Please address all correspondence to:

George W. Johnston
HLR Technology Corporation
Patent Law Department
340 Kingsland Street
Nutley, New Jersey 07110

Please direct all telephone calls to:

John P. Parise
(973) 235-6326

(16) A Duplicate of These Application Papers, Certified As Such

A certified duplicate is enclosed.

(17) An Oath or Declaration As Set Forth In Paragraph (b) of 37 C.F.R. § 1.740

Applicant attaches a declaration as set forth in 37 C.F.R. § 1.740(b), signed by an officer of HLR, the owner of record of U.S. Patent No. 4,598,089, who is authorized to practice before the Patent and Trademark Office and who has general authority to act on HLR's behalf in patent matters.

U.S. Patent No. 4,589,089
Issue Date: July 1, 1986

Request for Extension

Having included in this Application all of the requisite information under 35 U.S.C. § 156 and 37 C.F.R. § 1.740, Applicant requests an extension of U.S. Patent No. 4,598,089 for five (5) years days from June 18, 2004 to June 18, 2009, by reason of its claims encompassing orlistat and its salts and esters (if any) as a single entity or in combination with another active ingredient.

Respectfully submitted,

HLR TECHNOLOGY CORPORATION

By: George W. Johnston

George W. Johnston
Vice President
Registration No. 28,090

May 20, 1999
Date

U.S. Patent No. 4,589,089
Issue Date: July 1, 1986

Certification

The undersigned certifies that this Application for Extension of Patent Term Under 35 U.S.C. § 156 including its exhibits is being submitted as duplicate originals.

By: George W. Johnston

George W. Johnston
Vice President
Registration No. 28,090

Date: May 20, 1999

59220

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re United States Patent No. 4,598,089

Attn: Box Patent Ext.

Inventors: Hadvary et al.

Issue Date: July 1, 1986

For: Leucine Derivatives

TRANSMITTAL LETTER FOR APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. §156

Nutley, New Jersey 07110
May 20, 1999

Assistant Commissioner for Patents
Washington, D.C. 20231

S i r:

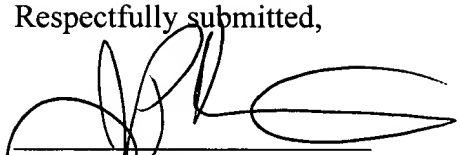
Transmitted herewith are the following: (a) Application for Extension of Patent Term Under 35 U.S.C. §156 with Exhibits (separately bound) and (b) Declaration and Power of Attorney for Application for Extension of Patent Term under 35 U.S.C. §156, for U.S. Patent No. 4,598,089. The Application is being submitted in duplicate, and the undersigned certifies that each copy of the attached Application is a duplicate original. In addition, three courtesy copies of all papers filed are being provided for the convenience of the Assistant Commissioner.

Please charge Deposit Account No. 08-2525 in the amount of $1120.00. The Commissioner is authorized to charge any additional fees, which may be required, or credit any overpayments to Account No. 08-2525.

U.S. Patent No. 4,598,089
Issue Date: July 1, 1986

A duplicate copy of this cover sheet is enclosed.

Respectfully submitted,



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59219

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re United States Patent No. 4,598,089 Attn: Box Patent Ext.

Inventors: Hadvary et al.

Issue Date: July 1, 1986

For: Leucine Derivatives

DECLARATION AND POWER OF ATTORNEY FOR APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. §156

Nutley, New Jersey 07110
May 20, 1999

Assistant Commissioner for Patents
Washington, D.C. 20231

S i r:

I, George W. Johnston, a Vice President of HLR Technology Corporation ("HLR"), which submits the attached Application for Extension of Patent Term Under 35 U.S.C. § 156, of the same date as this Declaration, declare that:

(1) HLR is the owner of record of U.S. Patent No. 4,598,089 and I am authorized to obligate HLR;

(2) I am a patent attorney authorized to practice before the Patent and Trademark Office and have general authority from HLR to act on its behalf in patent matters;

(3) I have reviewed and understand the contents of the Application being submitted for extension of the term of U.S. Patent No. 4,598,089 pursuant to 35 U.S.C. § 156 and 37 C.F.R. § 1.710 *et seq.*;

(4) I believe this patent is subject to extension under 35 U.S.C. § 156 and 37 C.F.R. § 1.710;

(5) I believe an extension of the length claimed is justified under 35 U.S.C. § 156 and the applicable regulations; and

(6) I believe the patent for which the extension is being sought meets the conditions for extension of the term of a patent as set forth in 35 U.S.C. § 156, and more particularly, in 37 C.F.R. § 1.720.

I hereby appoint the following attorneys as agents for HLR under 35 U.S.C. § 156 with the authority to sign, submit and prosecute this Application and transact all business in the Patent and Trademark Office and with the Secretary of Health and Human Services connected therewith: George W. Johnston (Reg. No. 28090), William H. Epstein (Reg. No. 20008), Dennis P. Tramaloni (Reg. No. 28542), Patricia S. Rocha-Tramaloni (Reg. No. 31054), and John P. Parise (Reg. No. 34403).

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I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this patent extension application or any extension of U.S. Patent No. 4,598,089.

Respectfully submitted,
HLR TECHNOLOGY CORPORATION

By: George W Johnston
George W Johnston
Vice President

Date: May 20, 1999

78386

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re United States Patent No. 4,598,089

Attn: Box Patent Ext.

Inventors: Hadvary et al.

Issue Date: July 1, 1986

For: Leucine Derivatives

EXHIBITS FOR

TRANSMITTAL LETTER FOR APPLICATION FOR

EXTENSION OF PATENT TERM UNDER 35 U.S.C. §156

Exhibit 1 .....Approved Physician Insert

Exhibit 2 .....FDA Approval Letter

Exhibit 3 .....U.S. Patent No. 4,598,089

Exhibit 4 .....Maintenance Fee Statments

Exhibit 5 .....IND Application & Receipt

Exhibit 6 .....NDA Application & Receipt

Exhibit 7 .....Chronology Listing of Regulatory Interactions for IND and NDA

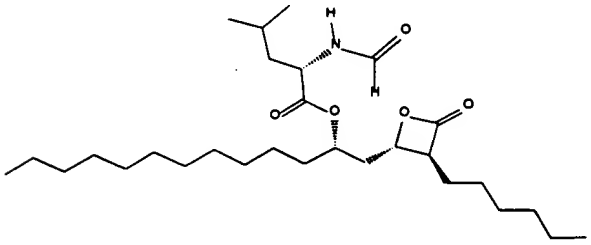
83110

Roche

XENICAL®
(orlistat)
CAPSULES

DESCRIPTION: XENICAL (orlistat) is a lipase inhibitor for obesity management that acts by inhibiting the absorption of dietary fats.

Orlistat is (S)-2-formylamino-4-methyl-pentanoic acid (S)-1-[[(2S, 3S)-3-hexyl-4-oxo-2-oxetanyl] methyl]-dodecyl ester. Its empirical formula is $C_{29}H_{53}NO_5$, and its molecular weight is 495.7. It is a single diastereomeric molecule that contains four chiral centers, with a negative optical rotation in ethanol at 529 nm. The structure is:



Orlistat is a white to off-white crystalline powder. Orlistat is practically insoluble in water, freely soluble in chloroform, and very soluble in methanol and ethanol. Orlistat has no pK_a within the physiological pH range.

XENICAL is available for oral administration in dark-blue, hard-gelatin capsules, with light-blue imprinting. Each capsule contains 120 mg of the active ingredient, orlistat. The capsules also contain the inactive ingredients microcrystalline cellulose, sodium starch glycolate, sodium lauryl sulfate, povidone, and talc. Each capsule shell contains gelatin, titanium dioxide, and FD&C Blue No.1, with printing of pharmaceutical glaze NF, titanium dioxide, and FD&C Blue No.1 aluminum lake.

CLINICAL PHARMACOLOGY: ***Mechanism of Action:*** Orlistat is a reversible inhibitor of lipases. It exerts its therapeutic activity in the lumen of the stomach and small intestine by forming a covalent bond with the active serine residue site of gastric and pancreatic lipases. The inactivated enzymes are thus unavailable to hydrolyze dietary fat in the form of triglycerides into absorbable free fatty acids and monoglycerides. As undigested triglycerides are not absorbed, the resulting caloric deficit may have a positive effect on weight control. Systemic absorption of the drug is therefore not needed for activity. At the recommended therapeutic dose of 120 mg three times a day, orlistat inhibits dietary fat absorption by approximately 30%.

Pharmacokinetics: *Absorption:* Systemic exposure to orlistat is minimal. Following oral dosing with 360 mg ^{14}C-orlistat, plasma radioactivity peaked at approximately 8 hours; plasma concentrations of intact orlistat were near the limits of detection (<5 ng/mL). In therapeutic studies involving monitoring of plasma samples, detection of intact orlistat in plasma was sporadic and concentrations were low (<10 ng/mL or 0.02 μM), without evidence of accumulation, and consistent with minimal absorption.

The average absolute bioavailability of intact orlistat was assessed in studies with male rats at oral doses of 150 and 1000 mg/kg/day and in male dogs at oral doses of 100 and 1000 mg/kg/day and found to be 0.12%, 0.59% in rats and 0.7%, 1.9% in dogs, respectively.

Distribution: In vitro orlistat was >99% bound to plasma proteins (lipoproteins and albumin were major binding proteins). Orlistat minimally partitioned into erythrocytes.

Metabolism: Based on animal data, it is likely that the metabolism of orlistat occurs mainly within the gastrointestinal wall. Based on an oral ^{14}C-orlistat mass balance study in obese patients, two metabolites, M1 (4-member lactone ring hydrolyzed) and M3 (M1 with N-formyl leucine moiety cleaved), accounted for approximately 42% of total radioactivity in plasma. M1 and M3 have an open β-lactone ring and extremely weak lipase inhibitory activity (1000- and 2500-fold less than orlistat, respectively). In view of this low inhibitory activity and the low plasma levels at the therapeutic dose (average of 26 ng/mL and 108 ng/mL for M1 and M3, respectively, 2 to 4 hours after a dose), these metabolites are considered pharmacologically inconsequential. The primary metabolite M1 had a short half-life (approximately 3 hours) whereas the secondary metabolite M3 disappeared at a slower rate (half-life approximately 13.5 hours). In obese patients, steady-state plasma levels of M1, but not M3, increased in proportion to orlistat doses.

Elimination: Following a single oral dose of 360 mg ^{14}C-orlistat in both normal weight and obese subjects, fecal excretion of the unabsorbed drug was found to be the major route of elimination. Orlistat and its M1 and M3 metabolites were also subject to biliary excretion. Approximately 97% of the administered radioactivity was excreted in feces; 83% of that was found to be unchanged orlistat. The cumulative renal excretion of total radioactivity was <2% of the given dose of 360 mg ^{14}C-orlistat. The time to reach complete excretion (fecal plus urinary) was 3 to 5 days. The disposition of orlistat appeared to be similar between normal weight and obese subjects. Based on limited data, the half-life of the absorbed orlistat is in the range of 1 to 2 hours.

Special Populations: Because the drug is minimally absorbed, studies in special populations (geriatric, pediatric, different races, patients with renal and hepatic insufficiency) were not conducted.

Drug-Drug Interactions: Drug-drug interaction studies indicate that XENICAL had no effect on pharmacokinetics and/or pharmacodynamics of alcohol, digoxin, glyburide, nifedipine (extended-release tablets), oral contraceptives, phenytoin, or warfarin. XENICAL induced a modest increase of the bioavailability and lipid-lowering effect of pravastatin (see CLINICAL STUDIES and PRECAUTIONS). Alcohol did not affect the pharmacodynamics of orlistat.

Other Short-term Studies: In several studies of up to 6-weeks duration, the effects of therapeutic doses of XENICAL on gastrointestinal and systemic physiological processes were assessed in normal-weight and obese subjects. Postprandial cholecystokinin plasma concentrations were lowered after multiple doses of XENICAL in two studies but not significantly different from placebo in two other experiments. There were no clinically significant changes observed in gallbladder motility, bile composition or lithogenicity, or colonic cell proliferation rate, and no clinically significant reduction of gastric emptying time or gastric acidity. In addition, no effects on plasma triglyceride levels or systemic lipases were observed with the administration of XENICAL in these studies. In a 3-week

study of 28 healthy male volunteers, XENICAL (120 mg three times a day) did not significantly affect the balance of calcium, magnesium, phosphorus, zinc, copper, and iron.

Dose-response Relationship: A simple maximum effect (E_{max}) model was used to define the dose-response curve of the relationship between XENICAL daily dose and fecal fat excretion as representative of gastrointestinal lipase inhibition. The dose-response curve demonstrated a steep portion for doses up to approximately 400 mg daily, followed by a plateau for higher doses. At doses greater than 120 mg three times a day, the percentage increase in effect was minimal.

CLINICAL STUDIES: Observational epidemiologic studies have established a relationship between obesity and visceral fat and the risks for cardiovascular disease, type 2 diabetes, certain forms of cancer, gallstones, certain respiratory disorders, and an increase in overall mortality. These studies suggest that weight loss, if maintained, may produce health benefits for obese patients who have or are at risk of developing weight-related comorbidities. The long-term effects of orlistat on morbidity and mortality associated with obesity have not been established.

The effects of XENICAL on weight loss, weight maintenance, and weight regain and on a number of comorbidities (eg, type 2 diabetes, lipids, blood pressure) were assessed in seven long-term (1- to 2-years duration) multicenter, double-blind, placebo-controlled clinical trials. During the first year of therapy, weight loss and weight maintenance were assessed. During the second year of therapy, some studies assessed continued weight loss and weight maintenance and others assessed the effect of orlistat on weight regain. These studies included over 2800 patients treated with XENICAL and 1400 patients treated with placebo. The majority of these patients had obesity-related risk factors and comorbidities. In these 7 studies, treatment with XENICAL and placebo designates treatment with XENICAL plus diet and placebo plus diet, respectively.

During the weight loss and weight maintenance period, a well-balanced, reduced-calorie diet that was intended to result in an approximate 20% decrease in caloric intake and provide 30% of calories from fat was recommended to all patients. In addition, all patients were offered nutritional counseling.

One-year Results: Weight Loss, Weight Maintenance, and Risk Factors: Weight loss was observed within 2 weeks of initiation of therapy and continued for 6 to 12 months.

Pooled data from five clinical trials indicated that the overall mean weight loss from randomization to the end of 6 months and 1 year of treatment in the intent-to-treat population were 12.4 lbs and 13.4 lbs in the patients treated with XENICAL and 6.2 lbs and 5.8 lbs in the placebo-treated patients, respectively. During the 4-week placebo lead-in period of the studies, an additional 5 to 6 lb weight loss was also observed in the same patients. Of the patients who completed 1 year of treatment, 57% of the patients treated with XENICAL (120 mg three times a day) and 31% of the placebo-treated patients lost at least 5% of their baseline body weight.

The percentages of patients achieving ≥5% and ≥10% weight loss after 1 year in five large multicenter studies for the intent-to-treat populations are presented in Table 1.

Table 1. Percentage of Patients Losing ≥5% and ≥10% of Body Weight From Randomization After 1-Year Treatment*

Intent-to-Treat Population†									
	≥5% Weight Loss					≥10% Weight Loss			
Study No.	XENICAL	n	Placebo	n	p-value	XENICAL	n	Placebo	n	p-value
14119B	35.5%	110	21.3%	108	0.021	16.4%	110	6.5%	108	0.022
14119C	54.8%	343	27.4%	340	<0.001	24.8%	343	8.2%	340	<0.001
14149	50.6%	241	26.3%	236	<0.001	22.8%	241	11.9%	236	0.02
14161‡	37.1%	210	16.0%	212	<0.001	19.5%	210	3.8%	212	<0.001
14185	42.6%	657	22.4%	223	<0.001	17.7%	657	9.9%	223	0.006

The diet utilized during year 1 was a reduced-calorie diet.

* Treatment designates XENICAL 120 mg three times a day plus diet or placebo plus diet

† Last observation carried forward

‡ All studies, with the exception of 14161, were conducted at centers specialized in treating obesity and complications of obesity. Study 14161 was conducted with primary care physicians.

The relative changes in risk factors associated with obesity following 1 year of therapy with XENICAL and placebo are presented for the population as a whole and for the population with abnormal values at randomization.

Population as a Whole: The changes in metabolic, cardiovascular and anthropometric risk factors associated with obesity based on pooled data for five clinical studies, regardless of the patient's risk factor status at randomization, are presented in Table 2. One year of therapy with XENICAL resulted in relative improvement in several risk factors.

Table 2. Mean Change in Risk Factors From Randomization Following 1-Year Treatment* Population as a Whole

Risk Factor	XENICAL 120 mg†	Placebo†
Metabolic:		
Total Cholesterol	-2.0%	+5.0%
LDL-Cholesterol	-4.0%	+5.0%
HDL-Cholesterol	+9.3%	+12.8%
LDL/HDL	-0.37	-0.20
Triglycerides	+1.34%	+2.9%
Fasting Glucose, mmol/L	-0.04	+0.0
Fasting Insulin, pmol/L	-6.7	+5.2
Cardiovascular:		
Systolic Blood Pressure, mm Hg	-1.01	+0.58
Diastolic Blood Pressure, mm Hg	-1.19	+0.46
Anthropometric:		
Waist Circumference, cm	-6.45	-4.04
Hip Circumference, cm	-5.31	-2.96

* Treatment designates XENICAL 120 mg three times a day plus diet or placebo plus diet

† Intent-to-treat population at week 52, observed data based on pooled data from 5 studies

Population With Abnormal Risk Factors at Randomization: The changes from randomization following 1-year treatment in the population with abnormal lipid levels (LDL ≥130 mg/dL, LDL/HDL ≥3.5, HDL <35 mg/dL) were greater for XENICAL compared to placebo with respect to LDL-cholesterol (-7.83% vs +1.14%) and the LDL/HDL ratio (-0.64 vs -0.46). HDL increased in the placebo group by 20.1% and in the XENICAL group by 18.8%. In the population with abnormal blood pressure at baseline (systolic BP ≥140 mm Hg), the change in SBP from randomization to 1 year was greater for XENICAL (-10.89 mm Hg) than placebo (-5.07 mm Hg). For patients with a diastolic blood pressure ≥90 mm Hg, XENICAL patients decreased by -7.9 mm Hg while the placebo patients decreased by -5.5 mm Hg. Fasting insulin decreased more for XENICAL than placebo (-39 vs -16 pmol/L) from randomization to 1 year in the population with abnormal baseline values (≥120 pmol/L). A greater reduction in waist circumference for XENICAL vs placebo (-7.29 vs -4.53 cm) was observed in the population with abnormal baseline values (≥100 cm).

Effect on Weight Regain: Three studies were designed to evaluate the effects of XENICAL compared to placebo in reducing weight regain after a previous weight loss achieved following either diet alone (one study, 14302) or prior treatment with XENICAL (two studies, 14119C and 14185). The diet utilized during the 1-year weight regain portion of the studies was a weight-maintenance diet, rather than a weight-loss diet, and patients received less nutritional counseling

than patients in weight-loss studies. For studies 14119C and 14185, patients' previous weight loss was due to 1 year of treatment with XENICAL in conjunction with a mildly hypocaloric diet. Study 14302 was conducted to evaluate the effects of 1 year of treatment with XENICAL on weight regain in patients who had lost 8% or more of their body weight in the previous 6 months on diet alone.

In study 14119C, patients treated with placebo regained 52% of the weight they had previously lost while the patients treated with XENICAL regained 26% of the weight they had previously lost ($p<0.001$). In study 14185, patients treated with placebo regained 63% of the weight they had previously lost while the patients treated with XENICAL regained 35% of the weight they had lost ($p<0.001$). In study 14302, patients treated with placebo regained 53% of the weight they had previously lost while the patients treated with XENICAL regained 32% of the weight that they had lost ($p<0.001$).

Two-year Results: Long-term Weight Control and Risk Factors: The treatment effects of XENICAL were examined for 2 years in four of the five 1-year weight management clinical studies previously discussed (see Table 1). At the end of year 1, the patients' diets were reviewed and changed where necessary. The diet prescribed in the second year was designed to maintain patient's current weight. XENICAL was shown to be more effective than placebo in long-term weight control in four large, multicenter, 2-year double-blind, placebo-controlled studies.

Pooled data from four clinical studies indicate that 40% of all patients treated with 120 mg three times a day of XENICAL and 24% of patients treated with placebo who completed 2 years of the same therapy had ≥5% loss of body weight from randomization. Pooled data from four clinical studies indicate that the relative weight loss advantage between XENICAL 120 mg three times a day and placebo treatment groups was the same after 2 years as for 1 year, indicating that the pharmacologic advantage of XENICAL was maintained over 2 years. In the same studies cited in the *One-year Results* (see Table 1), the percentages of patients achieving a ≥5% and ≥10% weight loss after 2 years are shown in Table 3.

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Table 3. Percentage of Patients Losing ≥5% and ≥10% of Body Weight From Randomization After 2-Year Treatment*

Intent-to-Treat Population**									
	≥5% Weight Loss					≥10% Weight Loss			
Study No.	XENICAL	n	Placebo	n	p-value	XENICAL	n	Placebo	n	p-value
14119C	45.1%	133	23.6%	123	<0.001	24.8%	133	6.5%	123	<0.001
14149	43.3%	178	27.2%	158	0.002	18.0%	178	9.5%	158	0.025
14161†	25.0%	148	15.0%	113	0.049	16.9%	148	3.5%	113	0.001
14185	34.0%	147	27.9%	122	0.279	17.7%	147	11.5%	122	0.154

The diet utilized during year 2 was designed for weight maintenance and not weight loss.

* Treatment designates XENICAL 120 mg three times a day plus diet or placebo plus diet

** Last observation carried forward

† All studies, with the exception of 14161 were conducted at centers specializing in treating obesity or complications of obesity. Study 14161 was conducted with primary care physicians.

The relative changes in risk factors associated with obesity following 2 years of therapy were also assessed in the population as a whole and the population with abnormal risk factors at randomization.

Population as a Whole: The relative differences in risk factors between treatment with XENICAL and placebo were similar to the results following 1 year of therapy for total cholesterol, LDL-cholesterol, LDL/HDL ratio, triglycerides, fasting glucose, fasting insulin, diastolic blood pressure, waist circumference, and hip circumference. The relative differences between treatment groups for HDL cholesterol and systolic blood pressure were less than that observed in the year one results.

Population With Abnormal Risk Factors at Randomization: The relative differences in risk factors between treatment with XENICAL and placebo were similar to the results following 1 year of therapy for LDL- and HDL-cholesterol, triglycerides, fasting insulin, diastolic blood pressure, and waist circumference. The relative differences between treatment groups for LDL/HDL ratio and isolated systolic blood pressure were less than that observed in the year one results.

Study of Patients With Type 2 Diabetes: A 1-year double-blind, placebo-controlled study in type 2 diabetics (N=321) stabilized on sulfonylureas was conducted. Thirty percent of patients treated with XENICAL achieved at least a 5% or greater reduction in body weight from randomization compared to 13% of the placebo-treated patients ($p<0.001$). Table 4 describes the changes over 1 year of treatment with XENICAL compared to placebo, in sulfonylurea usage and dose reduction as well as in hemoglobin HbA1c, fasting glucose, and insulin.

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Table 4. Mean Changes in Body Weight and Glycemic Control From Randomization Following 1-Year Treatment in Patients With Type 2 Diabetes

	XENICAL 120 mg* (n=162)	Placebo* (n=159)	Statistical Significance
% patients who discontinued dose of oral sulfonylurea	11.7%	7.5%	†
% patients who decreased dose of oral sulfonylurea	31.5%	21.4%	
Average reduction in sulfonylurea medication dose	-22.8%	-9.1%	†
Body weight change (lbs)	-8.9	-4.2	†
HbA1c	-0.18%	+0.28%	†
Fasting glucose, mmol/L	-0.02	+0.54	†
Fasting insulin, pmol/L	-19.68	-18.02	ns

Statistical significance based on intent-to-treat population, last observation carried forward.

* Treatment designates XENICAL 120 mg three times a day plus diet or placebo plus diet.

† Statistically significant ($p \leq 0.05$) based on intent-to-treat, last observation carried forward.

ns nonsignificant, $p > 0.05$

In addition, XENICAL (n=162) compared to placebo (n=159) was associated with significant lowering for total cholesterol (-1.0% vs +9.0%, $p \leq 0.05$), LDL-cholesterol (-3.0% vs +10.0%, $p \leq 0.05$), LDL/HDL ratio (-0.26 vs -0.02, $p \leq 0.05$) and triglycerides (+2.54% vs +16.2%, $p \leq 0.05$), respectively. For HDL cholesterol, there was a +6.49% increase on XENICAL and +8.6% increase on placebo, $p > 0.05$. Systolic blood pressure increased by +0.61 mm Hg on XENICAL and increased by +4.33 mm Hg on placebo, $p > 0.05$. Diastolic blood pressure decreased by -0.47 mm Hg for XENICAL and by -0.5 mm Hg for placebo, $p > 0.05$.

Glucose Tolerance in Obese Patients: Two-year studies that included oral glucose tolerance tests were conducted in obese patients not previously diagnosed or treated for type 2 diabetes and whose baseline oral glucose tolerance test (OGTT) status at randomization was either normal, impaired, or diabetic.

The progression from a normal OGTT at randomization to a diabetic or impaired OGTT following 2 years of treatment with XENICAL (n=251) or placebo (n=207) were compared. Following treatment with XENICAL, 0.0% and 7.2% of the patients progressed from normal to diabetic and normal to impaired, respectively, compared to 1.9% and 12.6% of the placebo treatment group, respectively.

In patients found to have an impaired OGTT at randomization, the percent of patients improving to normal or deteriorating to diabetic status following 1 and 2 years of treatment with XENICAL compared to placebo are presented. After 1 year of treatment, 45.8% of the placebo patients and 73% of the XENICAL patients had a normal oral glucose tolerance test while 10.4% of the placebo

patients and 2.6% of the XENICAL patients became diabetic. After 2 years of treatment, 50% of the placebo patients and 71.7% of the XENICAL patients had a normal oral glucose tolerance test while 7.5% of placebo patients were found to be diabetic and 1.7% of XENICAL patients were found to be diabetic after treatment.

INDICATIONS AND USAGE: XENICAL is indicated for obesity management including weight loss and weight maintenance when used in conjunction with a reduced-calorie diet. XENICAL is also indicated to reduce the risk for weight regain after prior weight loss. XENICAL is indicated for obese patients with an initial body mass index (BMI) ≥30 kg/m^2 or ≥27 kg/m^2 in the presence of other risk factors (e.g., hypertension, diabetes, dyslipidemia).

Table 5 illustrates body mass index (BMI) according to a variety of weights and heights. The BMI is calculated by dividing weight in kilograms by height in meters squared. For example, a person who weighs 180 lbs and is 5'5" would have a BMI of 30.

Table 5. Body Mass Index (BMI), kg/m^2*

HEIGHT (ft/in)	WEIGHT (lb)																				
	120	130	140	150	160	170	180	190	200	210	220	230	240	250	260	270	280	290	300	310	320
4'10"	25	27	29	31	34	36	38	40	42	44	46	48	50	52	54	57	59	61	63	65	67
4'11"	24	26	28	30	32	34	36	38	40	43	45	47	49	51	53	55	57	59	61	63	65
5'0"	23	25	27	29	31	33	35	37	39	41	43	45	47	49	51	53	55	57	59	61	63
5'1"	23	25	27	28	30	32	34	36	38	40	42	44	45	47	49	51	53	55	57	59	61
5'2"	22	24	26	27	29	31	33	35	37	38	40	42	44	46	48	49	51	53	55	57	59
5'3"	21	23	25	27	28	30	32	34	36	37	39	41	43	44	46	48	50	51	53	55	57
5'4"	21	22	24	26	28	29	31	33	34	36	38	40	41	43	45	46	48	50	52	53	55
5'5"	20	22	23	25	27	28	30	32	33	35	37	38	40	42	43	45	47	48	50	52	53
5'6"	19	21	23	24	26	27	29	31	32	34	36	37	39	40	42	44	45	47	49	50	52
5'7"	19	20	22	24	25	27	28	30	31	33	35	36	38	39	41	42	44	46	47	49	50
5'8"	18	20	21	23	24	26	27	29	30	32	34	35	37	38	40	41	43	44	46	47	49
5'9"	18	19	21	22	24	25	27	28	30	31	33	34	36	37	38	40	41	43	44	46	47
5'10"	17	19	20	22	23	24	26	27	29	30	32	33	35	36	37	39	40	42	43	45	46
5'11"	17	18	20	21	22	24	25	27	28	29	31	32	34	35	36	38	39	41	42	43	45
6'0"	16	18	19	20	22	23	24	26	27	29	30	31	33	34	35	37	38	39	41	42	43
6'1"	16	17	19	20	21	22	24	25	26	28	29	30	32	33	34	36	37	38	40	41	42
6'2"	15	17	18	19	21	22	23	24	26	27	28	30	31	32	33	35	36	37	39	40	41

* Conversion Factors:
Weight in lbs ÷ 2.2 = weight in kilograms (kg)
Height in inches × 0.0254 = height in meters (m)
1 foot = 12 inches

CONTRAINDICATIONS: XENICAL is contraindicated in patients with chronic malabsorption syndrome or cholestasis, and in patients with known hypersensitivity to XENICAL or to any component of this product.

WARNINGS: *Miscellaneous:* Organic causes of obesity (e.g., hypothyroidism) should be excluded before prescribing XENICAL.

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PRECAUTIONS: ***General:*** Patients should be advised to adhere to dietary guidelines (see DOSAGE AND ADMINISTRATION). Gastrointestinal events (see ADVERSE REACTIONS) may increase when XENICAL is taken with a diet high in fat (>30% total daily calories from fat). The daily intake of fat should be distributed over three main meals. If XENICAL is taken with any one meal very high in fat, the possibility of gastrointestinal effects increases.

Patients should be counseled to take a multivitamin supplement that contains fat-soluble vitamins to ensure adequate nutrition because XENICAL has been shown to reduce the absorption of some fat-soluble vitamins and beta-carotene. In addition, the levels of vitamin D and beta-carotene may be low in obese patients compared with non-obese subjects. The supplement should be taken once a day at least 2 hours before or after the administration of XENICAL, such as at bedtime.

Table 6 illustrates the percentage of patients on XENICAL and placebo who developed a low vitamin level on two or more consecutive visits during 1 and 2 years of therapy in studies in which patients were not previously receiving vitamin supplementation.

Table 6. Incidence of Low Vitamin Values on Two or More Consecutive Visits (Nonsupplemented Patients With Normal Baseline Values - First and Second Year)

	Placebo*	XENICAL*
Vitamin A	1.0%	2.2%
Vitamin D	6.6%	12.0%
Vitamin E	1.0%	5.8%
Beta-carotene	1.7%	6.1%

* Treatment designates placebo plus diet or XENICAL plus diet

Some patients may develop increased levels of urinary oxalate following treatment with XENICAL. Caution should be exercised when prescribing XENICAL to patients with a history of hyperoxaluria or calcium oxalate nephrolithiasis.

Weight-loss induction by XENICAL may be accompanied by improved metabolic control in diabetics, which might require a reduction in dose of oral hypoglycemic medication (e.g., sulfonylureas, metformin) or insulin (see CLINICAL STUDIES).

Misuse Potential: As with any weight-loss agent, the potential exists for misuse of XENICAL in inappropriate patient populations (eg, patients with anorexia nervosa or bulimia). See INDICATIONS AND USAGE for recommended prescribing guidelines.

Information for Patients: Patients should read the Patient Information before starting treatment with XENICAL and each time their prescription is renewed.

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Drug Interactions: *Alcohol:* In a multiple-dose study in 30 normal weight subjects, coadministration of XENICAL and 40 grams of alcohol (e.g., approximately 3 glasses of wine) did not result in alteration of alcohol pharmacokinetics, orlistat pharmacodynamics (fecal fat excretion), or systemic exposure to orlistat.

Cyclosporine: No drug interaction studies have been conducted with XENICAL and cyclosporine. Since changes in cyclosporine absorption have been reported with variations in dietary intake, caution is advised in the concomitant use of XENICAL plus diet in patients receiving cyclosporine therapy.

Digoxin: In 12 normal-weight subjects receiving XENICAL 120 mg three times a day for 6 days, XENICAL did not alter the pharmacokinetics of a single dose of digoxin.

Fat-soluble Vitamin Supplements and Analogues: A pharmacokinetic interaction study showed a 30% reduction in beta-carotene supplement absorption when concomitantly administered with XENICAL. XENICAL inhibited absorption of a vitamin E acetate supplement by approximately 60%. The effect of orlistat on the absorption of supplemental vitamin D, vitamin A, and nutritionally-derived vitamin K is not known at this time.

Glyburide: In 12 normal-weight subjects receiving orlistat 80 mg three times a day for 5 days, orlistat did not alter the pharmacokinetics or pharmacodynamics (blood glucose-lowering) of glyburide.

Nifedipine (extended-release tablets): In 17 normal-weight subjects receiving XENICAL 120 mg three times a day for 6 days, XENICAL did not alter the bioavailability of nifedipine (extended-release tablets).

Oral Contraceptives: In 20 normal-weight female subjects, the treatment of XENICAL 120 mg three times a day for 23 days resulted in no changes in the ovulation-suppressing action of oral contraceptives.

Phenytoin: In 12 normal-weight subjects receiving XENICAL 120 mg three times a day for 7 days, XENICAL did not alter the pharmacokinetics of a single 300-mg dose of phenytoin.

Pravastatin: In a parallel study of 24 normal-weight, mildly hypercholesterolemic subjects receiving XENICAL 120 mg three times a day for 10 days, the effect of XENICAL was additive to the lipid-lowering effect of pravastatin. Modest increases (approximately 30%) in pravastatin plasma concentrations were observed during coadministration with XENICAL.

Warfarin: In 12 normal-weight subjects, administration of XENICAL 120 mg three times a day for 16 days did not result in any change in either warfarin pharmacokinetics (both R- and S-enantiomers) or pharmacodynamics (prothrombin time and serum Factor VII). Although undercarboxylated osteocalcin, a marker of vitamin K nutritional status, was unaltered with XENICAL administration, vitamin K levels tended to decline in subjects taking XENICAL. Therefore, as vitamin K absorption may be decreased with XENICAL, patients on chronic stable doses of warfarin who are prescribed XENICAL should be monitored closely for changes in coagulation parameters.

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Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenicity studies in rats and mice did not show a carcinogenic potential for orlistat at doses up to 1000 mg/kg/day and 1500 mg/kg/day, respectively. For mice and rats, these doses are 38 and 46 times the daily human dose calculated on a area under concentration vs time curve basis of total drug-related material.

Orlistat had no detectable mutagenic or genotoxic activity as determined by the Ames test, a mammalian forward mutation assay (V79/HPRT), an in vitro clastogenesis assay in peripheral human lymphocytes, an unscheduled DNA synthesis assay (UDS) in rat hepatocytes in culture, and an in vivo mouse micronucleus test.

When given to rats at a dose of 400 mg/kg/day in a fertility and reproduction study, orlistat had no observable adverse effects. This dose is 12 times the daily human dose calculated on a body surface area (mg/m^2) basis.

Pregnancy: Teratogenic Effects: Pregnancy Category B. Teratogenicity studies were conducted in rats and rabbits at doses up to 800 mg/kg/day. Neither study showed embryotoxicity or teratogenicity. This dose is 23 and 47 times the daily human dose calculated on a body surface area (mg/m^2) basis for rats and rabbits, respectively.

The incidence of dilated cerebral ventricles was increased in the mid- and high-dose groups of the rat teratology study. These doses were 6 and 23 times the daily human dose calculated on a body surface area (mg/m^2) basis for the mid- and high-dose levels, respectively. This finding was not reproduced in two additional rat teratology studies at similar doses.

There are no adequate and well-controlled studies of XENICAL in pregnant women. Because animal reproductive studies are not always predictive of human response, XENICAL is not recommended for use during pregnancy.

Nursing Mothers: It is not known if orlistat is secreted in human milk. Therefore, XENICAL should not be taken by nursing women.

Pediatric Use: The safety and efficacy of XENICAL in pediatric patients have not been established.

Geriatric Use: Clinical studies of XENICAL did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently from younger patients.

ADVERSE REACTIONS: ***Commonly Observed*** (based on first year and second year data - XENICAL 120 mg three times a day versus placebo):

Gastrointestinal (GI) symptoms were the most commonly observed treatment-emergent adverse events associated with the use of XENICAL in double-blind, placebo-controlled clinical trials and are primarily a manifestation of the mechanism of action. (Commonly observed is defined as an incidence of ≥5% and an incidence in the XENICAL 120 mg group that is at least twice that of placebo.)

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Table 7. Commonly Observed Adverse Events

Adverse Event	Year 1		Year 2	
	XENICAL* % Patients (N=1913)	Placebo* % Patients (N=1466)	XENICAL* % Patients (N=613)	Placebo* % Patients (N=524)
Oily Spotting	26.6	1.3	4.4	0.2
Flatus with Discharge	23.9	1.4	2.1	0.2
Fecal Urgency	22.1	6.7	2.8	1.7
Fatty/Oily Stool	20.0	2.9	5.5	0.6
Oily Evacuation	11.9	0.8	2.3	0.2
Increased Defecation	10.8	4.1	2.6	0.8
Fecal Incontinence	7.7	0.9	1.8	0.2

*Treatment designates XENICAL three times a day plus diet or placebo plus diet

These and other commonly observed adverse reactions were generally mild and transient, and they decreased during the second year of treatment. In general, the first occurrence of these events was within 3 months of starting therapy. Overall, approximately 50% of all episodes of GI adverse events associated with orlistat treatment lasted for less than 1 week, and a majority lasted for no more than 4 weeks. However, GI adverse events may occur in some individuals over a period of 6 months or longer.

Discontinuation of Treatment: In controlled clinical trials, 8.8% of patients treated with XENICAL discontinued treatment due to adverse events, compared with 5.0% of placebo-treated patients. For XENICAL, the most common adverse events resulting in discontinuation of treatment were gastrointestinal.

Incidence in Controlled Clinical Trials: The following table lists other treatment-emergent adverse events from seven multicenter, double-blind, placebo-controlled clinical trials that occurred at a frequency of ≥2% among patients treated with XENICAL 120 mg three times a day and with an incidence that was greater than placebo during year 1 and year 2, regardless of relationship to study medication.

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Table 8. Other Treatment-Emergent Adverse Events From Seven Placebo-Controlled Clinical Trials

Body System/Adverse Event	Year 1		Year 2	
	XENICAL* % Patients (N=1913)	Placebo* % Patients (N=1466)	XENICAL* % Patients (N=613)	Placebo* % Patients (N=524)
Gastrointestinal System				
Abdominal Pain/Discomfort	25.5	21.4	-	-
Nausea	8.1	7.3	3.6	2.7
Infectious Diarrhea	5.3	4.4	-	-
Rectal Pain/Discomfort	5.2	4.0	3.3	1.9
Tooth Disorder	4.3	3.1	2.9	2.3
Gingival Disorder	4.1	2.9	2.0	1.5
Vomiting	3.8	3.5	-	-
Respiratory System				
Influenza	39.7	36.2	-	-
Upper Respiratory Infection	38.1	32.8	26.1	25.8
Lower Respiratory Infection	7.8	6.6	-	-
Ear, Nose & Throat Symptoms	2.0	1.6	-	-
Musculoskeletal System				
Back Pain	13.9	12.1	-	-
Pain Lower Extremities	-	-	10.8	10.3
Arthritis	5.4	4.8	-	-
Myalgia	4.2	3.3	-	-
Joint Disorder	2.3	2.2	-	-
Tendonitis	-	-	2.0	1.9
Central Nervous System				
Headache	30.6	27.6	-	-
Dizziness	5.2	5.0	-	-
Body as a Whole				
Fatigue	7.2	6.4	3.1	1.7
Sleep Disorder	3.9	3.3	-	-
Skin & Appendages				
Rash	4.3	4.0	-	-
Dry Skin	2.1	1.4	-	-
Reproductive, Female				
Menstrual Irregularity	9.8	7.5	-	-
Vaginitis	3.8	3.6	2.6	1.9
Urinary System				
Urinary Tract Infection	7.5	7.3	5.9	4.8
Psychiatric Disorder				
Psychiatric Anxiety	4.7	2.9	2.8	2.1
Depression	-	-	3.4	2.5

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Body System/Adverse Event	Year 1		Year 2	
	XENICAL* % Patients (N=1913)	Placebo* % Patients (N=1466)	XENICAL* % Patients (N=613)	Placebo* % Patients (N=524)
Hearing & Vestibular Disorders				
Otitis	4.3	3.4	2.9	2.5
Cardiovascular Disorders				
Pedal Edema	-	-	2.8	1.9

* Treatment designates XENICAL 120 mg three times a day plus diet or placebo plus diet

\- None reported at a frequency ≥2% and greater than placebo

OVERDOSAGE: Single doses of 800 mg XENICAL and multiple doses of up to 400 mg three times a day for 15 days have been studied in normal weight and obese subjects without significant adverse findings.

Should a significant overdose of XENICAL occur, it is recommended that the patient be observed for 24 hours. Based on human and animal studies, systemic effects attributable to the lipase-inhibiting properties of orlistat should be rapidly reversible.

DOSAGE AND ADMINISTRATION: The recommended dose of XENICAL is one 120 mg capsule three times a day with each main meal containing fat (during or up to 1 hour after the meal).

The patient should be on a nutritionally balanced, reduced-calorie diet that contains approximately 30% of calories from fat. The daily intake of fat, carbohydrate, and protein should be distributed over three main meals. If a meal is occasionally missed or contains no fat, the dose of XENICAL can be omitted.

Because XENICAL has been shown to reduce the absorption of some fat-soluble vitamins and beta-carotene, patients should be counseled to take a multivitamin containing fat-soluble vitamins to ensure adequate nutrition. The supplement should be taken at least 2 hours before or after the administration of XENICAL, such as at bedtime.

Doses above 120 mg three times a day have not been shown to provide additional benefit.

Based on fecal fat measurements, the effect of XENICAL is seen as soon as 24 to 48 hours after dosing. Upon discontinuation of therapy, fecal fat content usually returns to pretreatment levels within 48 to 72 hours.

The safety and effectiveness of XENICAL beyond 2 years have not been determined at this time.

HOW SUPPLIED: XENICAL is a dark-blue, hard-gelatin capsule containing pellets of powder.

XENICAL 120 mg Capsules: Dark-blue, two-piece, No. 1 opaque hard-gelatin capsule imprinted with Roche and XENICAL 120 in light-blue ink — bottle of 90 (NDC 0004-0256-52).

XENICAL® (orlistat)

Storage Conditions: **Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F)** [see USP Controlled Room Temperature]. **Keep bottle tightly closed.**

XENICAL should not be used after the given expiration date.

Pharmaceuticals

Roche Laboratories Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199

Revised: May 1999

Printed in USA

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-766

APR 23 1999

Hoffmann-La Roche
Attention: Ms. Peggy Jack
Program Director
Drug Regulatory Affairs
340 Kingsland Street
Nutley, NJ 07110-1199

Dear Ms. Jack:

Please refer to your new drug application (NDA) dated November 26, 1996, received November 27, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xenical (orlistat) Capsules, 120 mg.

We acknowledge receipt of your submissions dated May 12, 15, and 27, July 6, 15, 17, and 31, August 11, September 9, and October 7, 13, and 30, 1998; and January 6, 18, and 21(2), March 2, 11, 12, 22(2), 23, 24, 26, and 30, and April 1, 5, 7, and 23(2), 1999. Your submission of January 18, 1999, constituted a complete response to our May 12, 1998, action letter. The goal date for this application is July 19, 1999.

This new drug application provides for the use of Xenical (orlistat) Capsules for obesity management including weight loss and weight maintenance when used in conjunction with a reduced calorie diet. Xenical is also indicated to reduce the risk for weight regain after prior weight loss. Xenical is indicated for obese patients with an initial body mass index (BMI) $\geq$30 kg/m^2 or $\geq$27kg/m^2 in the presence of other risk factors (e.g., hypertension, diabetes, dyslipidemia).

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted April 23, 1999, patient package insert submitted April 23, 1999, and immediate container label submitted April 5, 1999). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material.

For administrative purposes, this submission should be designated "FPL for approved NDA 20-766." Approval of this submission by FDA is not required before the labeling is used.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

We remind you of your Phase 4 commitment specified in your submission dated April 23, 1999, to provide monthly updates of breast cancer diagnoses from the ongoing studies that were included in your January 18, 1999, submission. These updates will continue until these studies are completed.

As of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We note that you have not fulfilled the requirements of 21 CFR 314.55. We are deferring submission of your pediatric studies until 12/2/00. However, in the interim, please submit your pediatric drug development plans within 120 days from the date of this letter unless you believe a waiver is appropriate.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov.cder/pediatric) for details. If you wish to qualify for pediatric exclusivity, you should submit a "Proposed Pediatric Study Request" in addition to your plans for pediatric drug development described above. If you do not submit a Proposed Pediatric Study Request within 120 days from the date of this letter, we will presume that you are not interested in obtaining pediatric exclusivity [NOTE: You should still submit a pediatric drug development plan] and will notify you of the pediatric studies that are required under section 21 CFR 314.55. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity.

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Maureen Hess, MPH, RD, Regulatory Health Project Manager, at (301) 827-6411.

Sincerely,

James Bilstad, M.D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

United States Patent [19]

Hadvary et al.

[11] **Patent Number: 4,598,089**

[45] **Date of Patent: Jul. 1, 1986**

[54] **LEUCINE DERIVATIVES**

[75] Inventors: **Paul Hadvary**, Biel-Benken; **Erich Hochuli**, Arisdorf; **Ernst Kupfer**, Basel; **Hans Lengsfeld**, Reinach; **Ernst K. Weibel**, Pratteln, all of Switzerland

[73] Assignee: **Hoffmann-La Roche Inc.**, Nutley, N.J.

[21] Appl. No.: **621,827**

[22] Filed: **Jun. 18, 1984**

[30] **Foreign Application Priority Data**

Jun. 22, 1983 [CH] Switzerland 3415/83

[51] **Int. Cl.**[4] **C07D 305/12**; C12P 17/02; A61K 31/365

[52] **U.S. Cl.** **514/449**; 549/263; 549/328; 514/909; 435/123; 435/886

[58] **Field of Search** 549/263, 328; 435/123; 514/449

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,189,438	2/1980	Umezawa et al.	549/263
4,202,824	5/1980	Umezawa et al.	549/263
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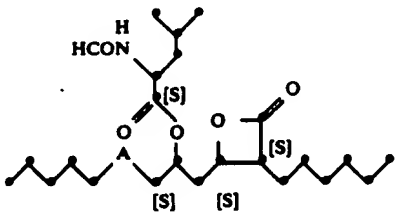
OTHER PUBLICATIONS

Derwent 70402 D/39 (Mar. 1980).
Derwent 87970 B/49 (May 1978).

Primary Examiner—Glennon H. Hollrah
Assistant Examiner—Dara Dinner
Attorney, Agent, or Firm—Jon S. Saxe; Bernard S. Leon; George W. Johnston

[57] **ABSTRACT**

Novel compounds of the formula



I

wherein A signifies the group

or $-(CH_2)_5-$,

which inhibit pancreas lipase and can be used for the control or prevention of obesity and hyperlipaemia, are disclosed. The inventive compounds can be produced by the cultivation of microorganism *Streptomyces toxytricini*, identified as NRRL 15443.

20 Claims, No Drawings

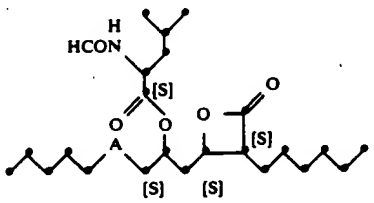
LEUCINE DERIVATIVES

BACKGROUND

The present invention concerns N-formylleucine derivatives which are useful in the treatment of obesity and hyperlipaemia.

SUMMARY OF THE INVENTION

The present invention is concerned with compounds of the formula

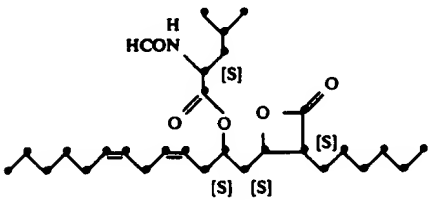


I

wherein A signifies the group

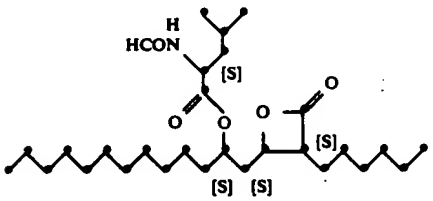
or $-(CH_2)_5-$.

Formula I above embraces (2S,3S,5S,7Z,10Z)-5-[(S)-2-formamido-4-methyl-valeryloxy]-2-hexyl-3-hydroxy-7,10-hexadecadienoic acid lactone of the formula



Ia

(i.e., lipstatin,) and (2S,3S,5S)-5-[(S)-2-formamido-4-methyl-valeranyloxy]-2-hexyl-3-hydroxy-hexadecanoic acid lactone of the formula



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(i.e., tetrahydrolipstatin).

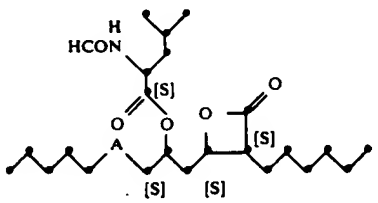
These compounds are novel and have valuable pharmacological properties. In particular, they inhibit pancreas lipase and can be used in the control or prevention of obesity and hyperlipaemia.

Objects of the present invention are the compounds of formula I above per se and as pharmaceutically active substances, the manufacture of these compounds, medicaments and industrially-produced foodstuffs containing a compound of formula I, their production as well as the use of these compounds in the control or prevention of illnesses. More particularly, the invention

concerns methods for preventing or treating obesity or hyperlipaemia in an afflicted mammal.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is concerned with compounds of the formula



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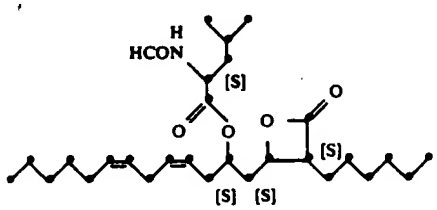
wherein A signifies the group

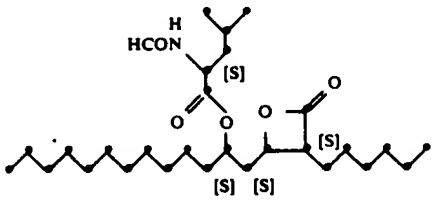
or $-(CH_2)_5-$.

Formula I above embraces (2S,3S,5S,7Z,10Z)-5-[(S)-2-formamido-4-methyl-valeryloxy]-2-hexyl-3-hydroxy-7,10-hexadecadienoic acid lactone of the formula



Ia

which is referred to hereinafter as lipstatin, and (2S,3S,5S)-5-[(S)-2-formamido-4-methyl-valeryloxy]-2-hexyl-3-hydroxy-hexadecanoic acid lactone of the formula



Ib

which is referred to hereinafter as tetrahydrolipstatin.

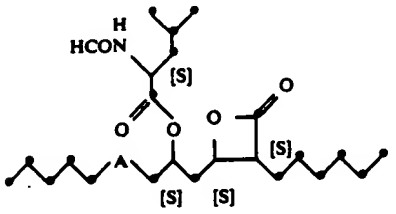
These compounds are novel and have valuable pharmacological proprties. In particular, they inhibit pancreas lipase and can be used in the control or prevention of obesity and hyperlipaemia.

The present invention is also concerned with pharmaceutical compositions for preventing and treating obesity or hyperlipaemia comprising a compound of formula I and a pharmaceutically acceptable carrier material.

The invention also concerns methods for preventing or treating obesity or hyperlipaemia in an afflicted mammal wherein compound I is administered to the mammal in an amount which is effective in preventing or treating obesity or hyperlipaemia.

The invention also is directed to a commercially-produced foodstuff comprising compound I admixed with a material suitable for consumption.

As used herein, [S] indicates the absolute configuration of compound I in the S-form. More particularly, the applicable carbon atoms in formula I having the S-configuration are noted with enlarged circles in the following formula:



wherein A is as above.

The digestion of fats (triglycerides) taken in with the food is effected in the intestine by pancreas lipase. The pancreas lipase cleaves the primary ester bonds of triglycerides, whereby free fatty acids and 2-monoglycerides result as products. These products can then be resorbed and utilized. By inhibiting the pancreas lipase the aforementioned cleavage of the foot fats and therewith also the resorption and utilization of these substances is partially prevented; the triglycerides are excreted in unchanged form.

The inhibition of pancreas lipase by the compounds of formula I can be demonstrated experimentally by registering tritrimetrically the oleic acid liberated in the cleavage of triolein by pig pancrease lipase. An emulsion which contains 1 mM taurodeoxycholate, 9 mM taurodeoleate, 0.1 mM cholesterol, 1 mM egg lecithin, 15 mg/ml BSA (i.e., bovine serum albumine), 2 mM Tris-HCl, 100 mM sodium chloride, 1 mM calcium chloride and the substrate triolein is treated with the compound of formula I dissolved in ethanol or dimethyl sulphoxide (10% of the emulsion volume) and the reaction is started by the addition of 100 µl (175 U) of pig pancreas lipase. the pH is held at 8 during the reaction by the addition of sodium hydroxide. The IC_{50} is calculated from the consumption of sodium hydroxide determined during 10 minutes. The IC_{50} is that concentration at which the lipase reactivity is inhibited to half of the maximum. Table I hereinafter contains IC_{50} values determined for the compounds of formula I and data concerning the acute toxicity (LD_{50} after single oral administration to mice).

TABLE I

Test compound	IC_{50} in µg/ml	LD_{50} in mg/kg p.o.
Lipstatin	0.07	>4000
Tetrahydrolipstatin	0.18	—

The inhibition of the resorption of fats taken in with the food, which is brought about by the inhibition of pancreas lipase, can be demonstrated in a double-labelling experiment on mice. For this purpose, there is administered to the test animals a test meal, which contains ^3H-triolein and ^{14}C-oleic acid, and a compound of formula I. By measuring the radioactivity there is then determined the amount of ^3H-triolein and ^{14}C-oleic acid (in % of the amount administered) excreted with the feces. The results set forth in Table II hereinafter show that in comparison to untreated control animals the excretion of unaltered triglyceride increases greatly and the excretion of oleic acid remains largely unchanged.

TABLE II

Test compound	Number of experimental animals	Dosage	Excretion in % of the amount administered: Triolein	Oleic acid
Controls	12	—	3.5 ± 0.3	10.1 ± 0.6
Lipstatin	6	40 mg/kg*	56.8 ± 13	13.8 ± 5.6

*The experiments were carried out with a preparation which contained about 10% lipstatin. The dosage specified is the amount of lipstatin administered.

The compounds of formula I can be manufactured in accordance with the invention by the following procedure:

(a) for the manufacture of the compound of formula Ia, aerobically cultivating a microorganism of the species Streptomyces toxytricini which produces this compound in an aqueous culture medium which contains suitable carbon and nitrogen sources and inorganic salts and separating the compound of formula Ia produced from the culture broth, or

(b) for the manufacture of the compound of formula Ib, hydrogenating the compound of formula Ia.

Streptomycetes strains which produce lipstatin, the compound of formula Ia, can be isolated from soil samples from various locations. An example is the microorganism isolated from a soil sample found in Mallorca, Spain, which was given the laboratory designation Streptomyces sp. 85–13 and which has been identified by CBS, Baarn (Netherlands) as *Streptomyces toxytricini* Preobrazhenskaya & Sveshnikova (see Bergey's Manual of Determinative Bacteriology, 8th Edition, page 811). It thereupon received the new designation Streptomyces toxytricini 85–13. A lyophilized sample of this strain was deposited on the 14th June 1983 at the Agricultural Research Culture Collection, Peoria, Ill., under the designation NRRL 15443.

A description of the identification of Streptomyces sp. 85–13 is given hereinafter:

Media

The composition of the media used is described in Int. J. Syst. Bacteriol 1966, 16, 3; 313–321.

Nonomura diagram

Nonomura used the results of the International Streptomyces Project (ISP) for the classification of the Streptomycetes speces (J. Ferment. Technol. 1974, 52, 2).

Colours

The names and code numbers of the aerial mycelium come from Tresner & Backus "System of color wheels for streptomycete taxonomy". The colours of the reverse of the colonies come from H. Prauser's selection from Baumann's "Farbtonkarte Atlas I".

Methodology

This was carried out according to the ISP methods (see Int. J. Syst. Bacteriol, 1966, 16, 3; 313–340).

I. Agar cultures after 16 days at 28° C. (double determination)

(a) Oatmeal agar

Growth: abundant; colonies: thin, spreading; aerial mycelium: velutinous, pinkish brown (Light Brown 57); reverse of the colonies: yellowish (Pr. Coo-3-m) with

broad purple-grey (Pr. Oc-6-x) margin; soluble pigments: doubtful.

(b) Starch-salt agar

Growth: good; colonies: thin, spreading; aerial mycelium: velutinous, pinkish brown (Light Brown 57) with white sectors; reverse of the colonies: dark straw coloured [Pr. Coo (Cr) 5a], margin and some other areas pinkish (Pr. Oc-5-b) with some dark reddish brown [Pr. O-5-S(r)] spots; soluble pigments: doubtful. The diastatic action is excellent.

(c) Glycerine-asparagine agar

Growth: good; colonies: thin, spreading; aerial mycelium: velutinous, pale pinkish brown (R4ec: Grayish Yellowish Pink); reverse of the colonies: orange (Pr. Oc-3-m/r); soluble pigments: pale pinkish brown.

(d) Yeast malt agar

Growth: good; colonies: thin, spreading; aerial mycelium: reddish brown (4ge: Light Grayish Reddish Brown 45); reverse of the colonies: yellow (Pr. Coo-4-5) and dark brown (Pr. Oc-5-r); soluble pigments: very pale yellowish brown.

II. Agar cultures after 62 days at 28° C. (double determination)

(a) Oatmeal agar

Growth: good; colonies: thin, spreading; aerial mycelium: powdery velutinous, cinnamon coloured [R-4ie: Light Brown (57)-Cork Tan] with broad, paler margin [R. 5gc: Light Reddish Brown (4.2)-Peach Tan]; reverse of the colonies: yellowish-brown with ochre-yellow (Pr. Coo-3-a) margin, slightly greyish towards the bright (Pr.Oc-4-r) centre; soluble pigments: pale ochre-brown.

(b) Starch-salt agar

As an oatmeal agar, but with a move greyish brown reverse (Pr. Oc-6-c) and with dark brown (Pr. Oc-4-r) spots and rings at the ends of the cross-hatches.

(c) Glycerine-asparagine agar

As on starch-salt agar, but paler light beige (5ec: Grayish yellowish Pink 32-Dusty Peach); Reverse: ochre-yellow [Pr. Coo (=Cr)-4-b], paler in the centre; no soluble pigments.

(d) Yeast-malt agar

Growth: fair; colonies: almost as on satmeal agar, but with very thin, pale grey margin; reverse: dark yellow (Pr. Coo-4-b), dark brown in submerginal areas; soluble pigments: doubtful.

III. Melanoid pigments

Peptone-yeast extract agar: negative after 24 hours, positive after 48 hours; tyrosine agar: positive after 24 hours, positive after 48 hours.

IV. Morphology of the sporulating aerial mycelium Section: spira-retinaculum apertum. Sympodial branched type. Spirals often irregular, with up to 5 coils often of different diameters.

V. Utilization of carbon sources No growth or only sparing growth on arabinose, xylose, inositol, mannitol, fructose, rhamnose, saccharose, raffinose.

VI. Spores

Oval to cylindrical-oval, sometimes of irregular size, smooth-walled. Spore chains with more than 10 spores.

VII. Nonomura diagram

R(Gy) 100 SRA sm(±) (±) (±)————

All Streptomycetes strains which produce the lipase inhibitor lipstatin are suitable for the purpose of the present invention, especially Streptomyces toxytricini 85-13, NRRL 15443, and its subcultures, mutants and variants.

The cultivation of these microorganisms for the manufacture of lipstatin can be carried out according to various fermentation methods. It can be carried out, for example, in shaking flasks or in 10 l or 200 l and 1000 l fermentors. A fixed amount of spore material or mycelium or a lipstatin-producing strain is introduced into a liquid medium which contains suitable carbon and nitrogen sources and salts required for the growth and the mixture is aerobically incubated at a temperature of 20°-37° C. for 1-6 days. Suitable carbon sources are, for example, dextrin, glucose, starch, ribose and glycerine. Suitable nitrogen sources are, for example, yeast extract, peptone or soya meal. Preferred salts are ammonium, magnesium and calcium salts. The fermentation is carried out at pH 6-8.

The isolation of the lipstatin is carried out according to methods which are known per se and which are familiar to any person skilled in the art. For example, it can be carried out as follows:

After completion of the fermentation the fermentation broth is centrifuged, whereupon 60-90% of the activity is found in the cell mass and the remainder is found in the centrifugate. The cell mass can then be treated with a lowr alcohol such as methanol and ethanol and extracted with the same solvent. The centrifugate can be extracted with a suitable organic solvent (e.g. with methylene chloride or ethyl acetate). The material produced from the extracts contains the desired lipstatin and can be enriched and purified by chromatographic methods. Suitable methods are, for example, multiplicative extraction with the system hexane/-methanol/water (50:40:9), filtration chromatography over silica gel while eluting with chloroform, column chromatography on silica gel while eluting with hexane, ethyl acetate and mixtures thereof, chromatography on apolar carrier materials while eluting with polar solvents such as methanol (reversed-phase chromatography) and high pressure liquid chromatography.

The Examples hereinaftr contain detail information relating to the cultivation of Streptomyces toxytricini 85-13 and the isolation of the lipstatin.

Tetrahydrolipstatin, the compound of formula Ib, can be manufactured by hydrogenating lipstatin in the presence of a suitable catalyst. Examples of catalysts which can be used are palladium/carbon, platinum oxide, palladium and the like. Suitable solvents are, for example, lower alcohols such as methanol and ethanol. The hy-

drogenation is preferably carried out at low hydrogen pressures and at room temperature (about 23° C.)

The compounds of formula I can be used as medicaments, for example in the form of pharmaceutical preparations. Illustratively, the pharmaceutical preparations can be administered orally, for example in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions. If desired, the compounds also can be administered parenterally.

For the manufacture of pharmaceutical preparations the compounds of formula I can be processed with pharmaceutically inert, inorganic or organic carriers. Examples of carriers which can be used for tablets, coated tablets, dragées and hard gelatine capsules are lactose, maize starch or derivatives thereof, talc, stearic acid or its salts and the like. Suitable carriers for soft gelatine capsules are, for example, vegetable oils, waxes, fats, semi-solid and liquid polyols and the like; depending on the nature of the active ingredient no carriers are, however, generally required in the case of soft gelatine capsules. Suitable carriers for the manufacture of solutions and syrups are, for example, water polyols, saccharose, invert sugar, glucose and the like.

Moreover, the pharmaceutical preparations can contain preserving agents, solubilizers, stabilizing agents, wetting agents, emulsifying agents, sweetening agents, colouring agents, flavouring agents, salts for varying the osmotic pressure, buffers, coating agents or antioxidants. They can also contain still other therapeutically valuable substances.

As mentioned earlier, medicaments containing a compound of formula I are also an object of the present invention as is a process for the manufacture of these medicaments, which process comprises bringing a compound of formula I and, if desired, one or more other therapeutically valuable substances into a galenical administration form. As mentioned earlier, the compounds of formula I can be used in the control or prevention of illnesses and especially in the control or prevention of obesity and hyperlipaemia. The dosage can vary within wide limits and is, of course, fitted to the individual requirements in each particular case. In general, in the case of oral administration a daily dosage of about 0.1 mg to 100 mg/kg body weight of compound I is appropriate.

Preferably, the pharmaceutical compositions of formula I in unit dosage form contain about 5% to 95% by weight of compound I to the total composition. A range of 10% to 50% is preferred.

The compounds of formula I can also be added to industrially-produced foodstuffs, especially to fats, oils, butter, margarine, chocolate and other confectionery goods. Such industrially-produced foodstuffs and their production are also objects of the present invention.

The following Examples illustrate the present invention in more detail, but are not intended to limit its extent. All temperatures are given in degrees Celsius (°C.). Room temperature is about 23° C. Unless otherwise indicated, precentages and ratios relating to solvents and expressed in volume, and the remaining percentages are expressed in weight. Unless indicated otherwise, all Examples were carried out as written. A Lobar column Lichoprep RP-8, size C, is a lowpressure reverse phase column, commercially available from Merck Co.

EXAMPLE 1

(a) Fermentation:

A shaking flask containing pre-culture medium 391 is inoculated with spores of Streptomyces toxytricini 85-13 (or vegetative mycelium thereof) and aerobically incubated as a shaking culture at 28° C. for 72 hours. About 2-5 vol.% of this culture is used to inoculate a fermentor preculture of 10 l containing pre-culture medium 391. Incubation is carried out at 28° for 3 days with aeration of 1 vvm and stirring at 400 rpm. This 10 l pre-culture is used to inoculate a 200 l production fermentor containing production medium N7. Fermentation is carried out at 28° for 124 hours with aeration of 1.0 vvm and stirring at 150 rpm. Regular analyses show after 124 hours an extracellular lipase-inhibiting activity of 53 IC_{50}/ml.

The pre-culture medium 391 (pH 7.0) has the following composition: 3% maize starch, 4% dextrin, 3% soya meal, 0.2% $(NH_4)_2SO_4$, 0.6% $CaCO_3$ and 0.8% soya oil. The pH was adjusted to 7. The production medium N 7 (pH 7.0) has the following composition: 1% potato starch, 0.5% glucose, 1% ribose, 0.5% glycerine, 0.2% peptone, 2% soya meal and 0.2% $(NH_4)_2SO_4$.

(b) Working-up:

The fermentation broth is centrifuged by means of a tube centrifuge, whereby there are obtained 175 l of culture filtrate and 12 kg of mycelium. The mycelium is discarded. The culture filtrate is heated to 80° for 10 minutes, cooled, again centrifuged and concentrafed to 50 l at 30° in vacuo. This concentrate is extracted with 50 l of hexane using a continuously operating extractor, the emulsion obtained is mixed with 50 l of hexane/ethyl acetate (1:1) and the organic phase is separated. This is dried ovr sodium sulphate and evaporated, there being obtained 199 g of crude extract I. The aqueous phase is diluted with water to 100 l and extracted with 100 l of ethyl acetate. After evaporation of the ethyl acetate solution, there are obtained 49 g of crude extract II. The aqueous phase is subsequently extracted once more with 100 l of ethyl acetate, whereby 78 g of crude extract III are obtained after evaporation.

(c) Purification:

The crude extracts II and III are filtered in three portions over in each case 1 kg of silica gel 60 (0.040-0.063 mm particle size), whereby the elution is carried out with chloroform (column: 10×100 cm). 18.3 g of enriched material are obtained in this manner. 178 g of this substance are again filtered over 1 kg of silica gel while eluting with chloroform. 5.29 g of active material are thus obtained. 802 mg of this substance are purified by reversed-phase chromatography on a commercially obtainable Lobar column (Lichoprep RP-8, size C) while eluting with methanol. There are obtained 158 mg of (2S,3S,5S,7Z,10Z)-5-[(S)-2-formamido-4-methyl-valeryloxy]-2-hexyl-3-hydroxy-7,10-hexadecadienoic acid lactone (lipstatin) which is a yellowish oil at room temperature. It is waxy-crystalline at low temperatures.

Microanalysis (dried for 20 hours in a high vacuum at 50°):

Calculated for $C_{29}H_{49}N_1O_5$ (491.713): C 70.84, H 10.04, N 2.85. Found C 70.85, H 9.97, N 2.59.

Optical rotation: $[\alpha]_D^{20} = -19.0°$ (c=1 in chloroform).

Mass spectrum (chemical ionization with NH_3 as the reagent gas): Peaks at, inter alia, m/z 509 ($M+NH_4^+$) and 492 ($M+H^+$).

IR spectrum (film): Bands at, inter alia, 3318, 3012, 2928, 2558, 2745, 1823, 1740, 1673, 1521, 1382, 1370, 1250, 1191 cm^{-1}.

The absolute configuration could be established by chemically degrading the lipstatin and comparing the fractions obtained with known substances.

EXAMPLE 2

(a) Fermentation

A 200 l fermentor containing production medium N 16 is inoculated with a pre-culture of Streptomyces toxytricini 85-13 (shaking flasks and then 10 l fermentation) prepared in accordance with Example 1. The production medium N 16 corresponds to production medium N 7 used in Example 1, but also contains 0.1% pig lard. The fermentation is carried out as described in Example 1 for 120 hours. After 120 hours, the intracellular lipase-inhibiting activity amounts to 71 IC_{50}/ml of fermentation broth and the extracellular lipase-inhibiting activity amounts to 4 IC_{50}/ml of fermentation broth.

(b) Working-up

After completion of the fermentation, the fermentation broth is heated to 80° for 10 minutes, subsequently cooled and the cell mass is separated using a tube centrifuge. By two-fold centrifugation there are obtained 11.4 kg of mycelium; the culture filtrate is discarded. The mycelium is triturated in 70 l of methanol for 30 minutes, whereupon the suspension obtained is suction filtered. The filter cake is again triturated with 50 l of methanol and suction filtered. The combined methanolic extracts are concentrated to 1.8 l. This concentrate is extracted three times with 2 l of butyl acetate each time. 160 g of crude extract are obtained from the combined organic phases after evaporation.

(c) Purification

This crude extract is purified by multiplicative extraction with the system hexane/methanol/water (5:4:0:9). The active substance is firstly transferred from the lower phase (lp) into the upper phase (up). 160 g of crude extract are dissolved in 4 l of lp and stirred in a stirring vessel with 4 l of up. After separating the up, the lp is extracted a second time with 4 l of fresh up. A stable emulsion forms and to this there are added 4 l of lp and 4 l of up, whereupon a good phase separation is achieved. After separating the up, the lp is extracted twice more with 8 l of fresh up. The combined up give 90.3 g of extract after evaporation. The extraction lp is discarded. The active substance is now transferred from the up into the lp. 90.3 g of the above extract are dissolved in 4 l of up and extracted with 4 l of lp. After phase separation, the up is extracted a further three times with fresh lp. The up is subsequently discarded. The combined lp are concebtrated to 0.7 l of aqueous phase and this is extracted eight times with a total of 0.2 l of ethyl acetate. 25.8 g of product are obtained after evaporation. The extracted aqueous phase is discarded. The further purification of this material is carried out by filtration over 1 kg of silica gel 60 (0.040–0.063 mm particle size; column 10×100 cm) while eluting with chloroform. There are obtained 649 mg of product which is chromatographed on a Lobar column (Lichoprep RP-8, size C) while eluting with methanol (reversed-phase chromatography). There are obtained 204 mg of lipstatin which is pure according to thin-layer chromatography.

EXAMPLE 3

138 mg of lipstatin are dissolved in 10 ml of ethanol and the solution is treated with 60 mg of 5 percent palladium/carbon and stirred at room temperature for 3 hours in a hydrogen atmosphere (balloon). The catalyst is subsequently centrifuged off. The hydrogenation product is chromatographed over a short silica gel column (1×5 cm) with chloroform. There are obtained 112 mg of (2S,3S,5S)-5-[(S)-2-formamido-4-methylvaleryloxy]-2-hexyl-3-hydroxyhexadecanoic acid lactone (tetrahydrolipstatin) as a waxy, slightly yellow solid.

Optical rotation: $[\alpha]_D^{20} = -32.0°$ (c=1 in chloroform).

Mass spectrum (chemical ionization with NH_3 is the reagent gas): Peaks at, inter alia, m/z 513 ($M+NH_4^+$); 496 ($M+H^+$) and 452 ($M+H^+-CO_2$).

IR spectrum (film): Bands at, inter alia, 3332, 2956, 2921, 2853, 1838, 1731, 1709, 1680, 1665, 1524, 1383, 1249 and 1200 cm^{-1}.

^{1}H-NMR spectrum (270 MHz, $CDCl_3$): 0.89 (6H); 0.97 (6H); 1.15-1.5 (27H); 1.5-1.85 (6H); 1.9-2.25 (2H); 3.24 (1H); 4.32 (1H); 4.68 (1H); 5.03 (1H); 6.43 (1H); 8.07 and 8.21 (1H) ppm.

EXAMPLE 4

(a) Fermentation

A 2 l shaking culture flask containing pre-culture medium 391 is inoculated with spores of an agar slant culture of Streptomyces toxytricini 85-13 and aerobically incubated at 28° C. for 72 hours. Thereafter, the 2 l preculture is transferred into a 50 l fermentor containing production medium N 16 and incubated at 28° C. for 77 hours with 0.5 vvm aeration. This 50 l pre-culture is used to inoculate a 1000 l fermentor containing medium N 16. This production fermentation is carried out at 28° C. and 0.5 vvm aeration for 91 hours, whereby a lipstatin titre of 73 IC_{50}/ml intracellularly and 16 IC_{50}/ml extracellularly is achieved. The entire fermentation broth is cooled to 2° C. and centrifuged, whereby there are obtained 41 kg of moist biomass which are frozen at −20° C.

(b) Working-up

37 kg of mycelium are melted at 4° C. and homogenized with about 40 l of water in a mixer. The thinly liquid suspension obtained is treated with 140 l of methanol and stirred for 20 minutes. The mixture is subsequently suction filtered over a cloth filter, whereupon the filter cake is extracted further with 140 l of methanol. The methanol extracts are concentrated at 30° C. to about 22 l. The concentrate obtained is diluted with ater to 50 l and extracted three times in a stirring vessel with 50 l of hexane/ethyl acetate (1:1) each time. In the second and third extractions there are obtained emulsions which can be broken by the addition of about 1.4 kg and 0.5 kg of sodium chloride, respectively. The combined organic extracts are concentrated, dried over sodium sulphate and evaporated to an oily residue. 428 g of crude extract are obtained.

(c) Purification

This crude extract is filtered in four portions over in each case 1 kg of silica gel 60 (0.040–0.063 mm particle

size), whereby the elution is carried out with chloroform (column: 10×100 cm). There are obtained 70 g of enriched preparation which is filtered in two portions over in each case 1 kg of silica gel 60 while eluting with hexane/ethyl acetate (gradient from 9:1 to 4:1). There are obtained 4.2 g of active material which is purified in four portions by reversed-phase chromatography on a Lobar column (Lichoprep RP-8, size C) while eluting with methanol. 1.77 g of lipstatin are obtained.

EXAMPLE A

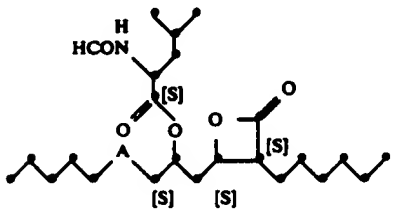
Manufacture of soft gelatine capsules of the following composition:

	Amount per capsule
Lipstatin	50 mg
NEOBEE M-5	450 µl

The solution of the active substance in NEOBEE M-5 is filled into soft gelatine capsules of suitable size. NEOBEE M-5 is a mixture of triglycerides commonly used for pharmaceutical preparations.

We claim:

1. A compound of the formula



wherein A is the group

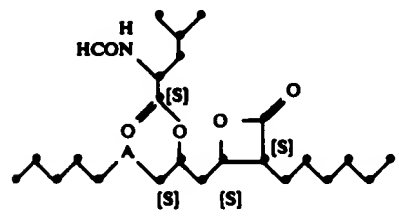
or $-(CH_2)_5-$.

2. The compound of claim 1, (2S,3S,5S,7Z,10Z)-5-[(S)-2-formamido-4-methyl-valeryloxy]-2-hexyl-3-hydroxy-7,10-hexadecadienoic 1,3 acid lactone.

3. The compound of claim 1, (2S,3S,5S)-5-[(S)-2-formamido-4-methyl-valeryloxy]-2-hexyl-3-hydroxy-hexadecanoic 1,3 acid lactone.

4. A pharmaceutical composition for administration to a patient comprising

(a) about 5% to about 95% of a compound of formula



wherein A is the group

or $-(CH_2)_5-$

said composition being present in a amount sufficient to supply about 0.1 to about 100 mg of compound I per kilogram of body weight of the patient per day; and

(b) 5% to 95% of a pharmaceutically acceptable inert carrier material, said composition being formulated in a unit dosage form.

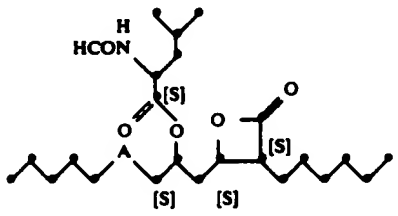
5. The composition of claim 4 wherein said composition is formulated in an oral unit dosage form.

6. The composition of claim 5 wherein said oral unit dosage form is a tablet, dragee, capsule, solution, emulsion or suspension.

7. The composition of claim 4 wherein compound I is (2S,3S,5S,7Z,10Z)-5-[(S)-2-formamido-4-methyl-valeryloxy]-2-hexyl-3-hydroxy-7,10-hexadecadienoic 1,3 acid lactone.

8. The composition of claim 4 wherein compound I is (2S,3S,5S)-5-[(S)-2-formamido-4-methyl-valeryloxy]-2-hexyl-3-hydroxy-hexadecanoic 1,3 acid lactone.

9. A method of treating obesity in an afflicted mammal comprising administering to the mammal a compound of the formula



wherein A is the group

or $-(CH_2)_5-$

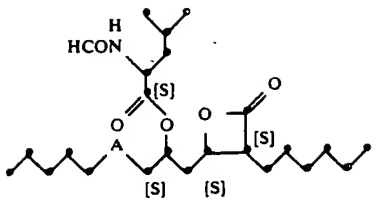
in an amount which is effective in treating obesity.

10. The method of claim 9 wherein compound I is (2S,3S,5S,7Z,10Z)-5-[(S)-2-formamido-4-methyl-valeryloxy]-2-hexyl-3-hydroxy-7,10-hexadecadienoic 1,3 acid lactone.

11. The method of claim 9 wherein compound I is (2S,3S,5S)-5-[(S)-2-formamido-4-methyl-valeryloxy]-2-hexyl-3-hydroxy-hexadecanoic 1,3 acid lactone.

12. The method of claim 9 wherein compound I is administered in a daily dose of about 0.1 mg to 100 mg/kg body weight of the mammal.

13. A method of treating hyperlipaemia in an afflicted mammal comprising adminstering to the mammal a compound of the formula



wherein A is the group

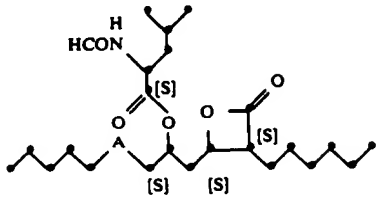
or $-(CH_2)_5-$,
in an amount which is effective in treating hyperlipaemia.

14. The method of claim 13 wherein compound I is (2S,3S,5S,7Z,10Z)-5-[(S)-2-formamido-4-methyl-valeryloxy]-2-hexyl-3-hydroxy-7,10-hexadecadienoic 1,3 acid lactone.

15. The method of claim 13 wherein compound I is (2S,3S,5S)-5-[(S)-2-formamido-4-methyl-valeryloxy]-2-hexyl-3-hydroxy-hexadecanoic 1,3 acid lactone.

16. The method of claim 13 wherein compound I is administered in a daily dose of about 0.1 mg to 100 mg/kg body weight of the mammal.

17. A method of preventing obesity in a mammal comprising administering to the mammal a compound of the formula



wherein A is the group

or $-(CH_2)_5-$,
in an amount which is effective in preventing obesity by inhibiting pancrease lipase.

18. The method of claim 17 wherein compound I is (2S,3S,5S,7Z,10Z)-5-[(S)-2-Formamido-4-methyl-valeryloxy]-2-hexyl-3-hydroxy-7,10-hexadecadienoic 1,3 acid lactone.

19. The method of claim 17 wherein compound I is (2S,3S,5S)-5-[(S)-2-formamido-4-methyl-valeryloxy]-2-hexyl-3-hydroxy-hexadecanoic 1,3 acid lactone.

20. The method of claim 17 wherein compound I is administered in a daily dose of about 0.1 mg to 100 mg/kg body weight of the mammal.

* * * * *

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1	4,598,089	185	3160	----	06/621,827	07/01/86	06/18/84	12	NO	PAID

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036291

MAINTENANCE FEE STATEMENT

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 10, "status" below.

If a maintenance fee payment is defective, the reason is indicated by code in column 10, "status" below. An explanation of the codes appears on the reverse of the Maintenance Fee Statement. TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(k) and (l).

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

ITM NBR	PATENT NUMBER	FEE CDE	FEE AMOUNT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	4,336,253	171	495	----	06/277,569	07/06/82	06/25/81	08	NO	PAID
2	[redacted]	173	490	----	06/621,827	07/01/86	06/18/84	04	NO	PAID
3	4,598,160	173	490	----	06/710,193	07/01/86	03/11/85	04	NO	PAID
4	4,599,316	173	490	----	06/557,710	07/08/86	12/02/83	04	NO	PAID
5	4,599,330	170	245	----	06/379,385	07/08/86	05/17/82	04	NO	PAID

Copy Sent to
Department Pat

If the "status" column for a patent number listed above does not indicate "PAID" a code or an asterisk (*) will appear in the "status" column. Where an asterisk (*) appears, the codes are set out below by the related item number. An explanation of the codes indicated in the "status" column and as set out below by the related item number appears on the reverse of the maintenance fee statement.

ITM NBR	ATTY DKT NUMBER
1	6232
2	RAN4039/42
3	6744
4	6574

DIRECT THE RESPONSE TOGETHER WITH PART B OF THIS NOTICE, AND ANY QUESTIONS ABOUT THIS NOTICE TO:
COMMISSIONER OF PATENTS AND TRADEMARKS, BOX M. FEE, WASHINGTON, DC 20231

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

APR 18 1988

IND 31,617

Hoffmann-La Roche Inc.
340 Kingsland Street
Nutley, New Jersey 07110

Dear Sir/Madam:

We are pleased to acknowledge receipt of your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act. Please note the following identifying data:

IND number assigned: 31,617

Sponsor: Hoffmann-La Roche Inc.

Name of Drug: Ro 18-0647-Tetrahydrolipstatin

Date of Submission: May 12, 1988

Date of Receipt: May 13, 1988

IT IS UNDERSTOOD THAT STUDIES IN HUMANS WILL NOT BE INITIATED UNTIL 30 DAYS AFTER THE DATE OF RECEIPT SHOWN ABOVE. If, within the 30 day period, we notify you of serious deficiencies that require correction before human studies can begin or that would require restriction of human studies until correction, it is understood that you will continue to withhold or restrict such studies until you are notified that the material you have submitted to correct the deficiencies is satisfactory.

You are responsible for compliance with the Federal Food, Drug and Cosmetic Act and Regulations. This responsibility includes the immediate reporting of any alarming adverse reactions in either animal or human studies, and submission of progress reports at intervals not to exceed one year.

IND 31,617

As sponsor of the clinical study proposed under this IND, you are now free to obtain supplies of the investigational drug.

Please forward all future communications concerning this IND in TRIPLICATE, IDENTIFIED WITH THIS IND NUMBER and addressed as follows:

Food and Drug Administration
Center for Drug Evaluation and Research, HFD-510
Attention: DOCUMENT CONTROL ROOM 14B03
5600 Fishers Lane
Rockville, Maryland 20857

Should you have any questions concerning this IND, please call me at (301) 443-3510 .

Sincerely yours,

Rita L. Hassall

Consumer Safety Officer
Division of Metabolism and Endocrine
Drug Products
Center for Drug Evaluation and Research

cc: Arch. File - pink
Division File - yellow
Division CSO - blue

ACKNOWLEDGEMENT

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

INVESTIGATIONAL NEW DRUG APPLICATION (IND)
(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) Part 312)

Form Approved. OMB No. 0910-0014
Expiration Date: November 30, 1987

NOTE: No drug may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40).

1. NAME OF SPONSOR
Hoffmann-La Roche Inc.

2. DATE OF SUBMISSION
May 12, 1988

3. ADDRESS *(Number, Street, City, State and Zip Code)*
340 Kingsland Street
Nutley, New Jersey 07110

4. TELEPHONE NUMBER *(Include Area Code)*
(201) 235-4692

5. NAME(S) OF DRUG *(Include all available names: Trade, Generic, Chemical, Code)*
(S)-1-[[(2S,3S)-3-Hexyl-4-oxo-2-oxetanyl]methyl] dodecyl(S)-2-formamido-4-methylvalerate - OR - Ro 18-0647 tetrahydrolipstatin

6. IND NUMBER *(If previously assigned)*

7. INDICATION(S) *(Covered by this submission)*
inhibitor of pancreatic lipase, the key enzyme necessary for the absorption of dietary triglycerides

8. PHASE (S) OF CLINICAL INVESTIGATION TO BE CONDUCTED: ☐ PHASE 1 ☒ PHASE 2 ☐ PHASE 3 ☐ OTHER _____ *(Specify)*

9. LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS *(21 CFR Part 312)*, NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, DRUG MASTER FILES *(21 CFR 314.420)*, AND PRODUCT LICENSE APPLICATIONS *(21 CFR Part 601)* REFERRED TO IN THIS APPLICATION.

10. SERIAL NUMBER
0 0 0

IND submissions should be consecutively numbered. The initial IND should be numbered "Serial Number: 000." The next submission (i.e., amendment, report, or correspondence) should be numbered "Serial Number: 001." Subsequent submissions should be numbered consecutively in the order in which they are submitted.

11. THIS SUBMISSION CONTAINS THE FOLLOWING: *(Check all that apply)*

☒ INITIAL INVESTIGATIONAL NEW DRUG APPLICATION (IND)

PROTOCOL AMENDMENT(S)
- ☐ NEW PROTOCOL
- ☐ CHANGE IN PROTOCOL
- ☐ NEW INVESTIGATOR

INFORMATION AMENDMENT(S):
- ☐ CHEMISTRY,MICROBIOLOGY
- ☐ PHARMACOLOGY/TOXICOLOGY
- ☐ CLINICAL

IND SAFETY REPORT(S)
- ☐ INITIAL WRITTEN REPORT
- ☐ FOLLOW-UP TO A WRITTEN REPORT

☐ RESPONSE TO FDA REQUEST FOR INFORMATION ☐ ANNUAL REPORT ☐ RESPONSE TO CLINICAL HOLD

☐ GENERAL CORRESPONDENCE ☐ REQUEST FOR REINSTATEMENT OF IND THAT IS WITHDRAWN, INACTIVATED, TERMINATED OR DISCONTINUED ☐ OTHER _____ *(Specify)*

Refer to the designated CFR citations before checking any of the following:

☐ TREATMENT IND 21 CFR 312.35(b) ☐ TREATMENT PROTOCOL 21 CFR 312.35(a) ☐ CHARGE REQUEST NOTIFICATION 21 CFR 312.7(c)

FOR FDA USE ONLY

CDR/DBIND/DGD RECEIPT STAMP	DDR RECEIPT STAMP	IND NUMBER ASSIGNED
		DIVISION ASSIGNMENT

FORM FDA 1571 (8/87) PREVIOUS EDITION IS OBSOLETE

HLR No: 88355
MJJ:id

Division of Metabolism & Endocrine Drug Products
HFN-810

12. **CONTENTS OF APPLICATION**

This application contains the following items: *(check all that apply)*

- [X] 1. Form FDA 1571 *[21 CFR 312.23 (a) (1)]*
- [X] 2. Table of contents *[21 CFR 312.23 (a) (2)]*
- [X] 3. Introductory statement *[21 CFR 312.23 (a) (3)]*
- [X] 4. General investigational plan *[21 CFR 312.23 (a) (3)]*
- [X] 5. Investigator's brochure *[21 CFR 312.23 (a) (5)]*
- 6. Protocol(s) *[21 CFR 312.23 (a) (6)]*
  - [X] a. Study protocol(s) *[21 CFR 312.23 (a) (6)]*
  - [X] b. Investigator data *[21 CFR 312.23 (a) (6)(iii)(b)]* or completed Form(s) FDA 1572
  - [X] c. Facilities data *[21 CFR 312.23 (a) (6)(iii)(b)]* or completed Form(s) FDA 1572
  - [X] d. Institutional Review Board data *[21 CFR 312.23 (a) (6)(iii)(b)]* or completed Form(s) FDA 1572
- [X] 7. Chemistry, manufacturing, and control data *[21 CFR 312.23 (a) (7)]*
  - [X] a. Environmental assessment or claim for exclusion *[21 CFR 312.23 (a) (7)(iv)(e)]*
- [X] 8. Pharmacology and toxicology data *[21 CFR 312.23 (a) (8)]*
- [X] 9. Previous human experience *[21 CFR 312.23 (a) (9)]*
- [ ] 10. Additional information *[21 CFR 312.23 (a) (10)]*

13 IS ANY PART OF THE CLINICAL STUDY TO BE CONDUCTED BY A CONTRACT RESEARCH ORGANIZATION? ☐ YES ☒ NO

IF YES, WILL ANY SPONSOR OBLIGATIONS BE TRANSFERRED TO THE CONTRACT RESEARCH ORGANIZATION? ☐ YES ☐ NO

IF YES, ATTACH A STATEMENT CONTAINING THE NAME AND ADDRESS OF THE CONTRACT RESEARCH ORGANIZATION, IDENTIFICATION OF THE CLINICAL STUDY, AND A LISTING OF THE OBLIGATIONS TRANSFERRED.

14 NAME AND TITLE OF THE PERSON RESPONSIBLE FOR MONITORING THE CONDUCT AND PROGRESS OF THE CLINICAL INVESTIGATIONS

Alan W. Dunton, M.D.
Director, Clinical Pharmacology Unit
Newark Beth Israel Hospital

15 NAME(S) AND TITLE(S) OF THE PERSON(S) RESPONSIBLE FOR REVIEW AND EVALUATION OF INFORMATION RELEVANT TO THE SAFETY OF THE DRUG

Johnathan B. Hauptman, M.D.
Director, Clinical Investigation
Hoffmann-La Roche Inc.

I agree not to begin clinical investigations until 30 days after FDA's receipt of the IND or on earlier notification by FDA. I also agree not to begin or continue clinical investigations covered by the IND if those studies are placed on clinical hold. I agree that an Institutional Review Board (IRB) that complies with the requirements set forth in 21 CFR Part 56 will be responsible for the initial and continuing review and approval of each of the studies in the proposed clinical investigation. I agree to conduct the investigation in accordance with all other applicable regulatory requirements.

16 NAME OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE	17 SIGNATURE OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE	
Margaret J. Jack	Margaret J Jack	
18 ADDRESS *(Number, Street, City, State and Zip Code)*	19 TELEPHONE NUMBER *(Include Area Code)*	20. DATE
Hoffmann-La Roche Inc. 340 Kingsland Street Nutley, New Jersey 07110	(201) 235-4692	May 20, 1988

(WARNING: A willfully false statement is a criminal offense U S C Title 18, Sec 1001)

Receipt Copy

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
INVESTIGATIONAL NEW DRUG APPLICATION (IND)
(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) Part 312)

Form Approved. OMB No. 0910-0014
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Hoffmann-La Roche Inc.

2. DATE OF SUBMISSION
May 12, 1988

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340 Kingsland Street
Nutley, New Jersey 07110

4. TELEPHONE NUMBER *(Include Area Code)*
(201) 235-4692

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FOR FDA USE ONLY

CDR/DBIND/DGD RECEIPT STAMP	DDR RECEIPT STAMP	IND NUMBER ASSIGNED
MAY 13 19[illegible]		
CENTRAL DOCUMENTS [illegible]		DIVISION ASSIGNMENT

FORM FDA 1571 (8/87) PREVIOUS EDITION IS OBSOLETE

HLR No: 88355
MJJ:jd

Division of Metabolism & Endocrine Drug Products
HFN-810

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Margaret J. Jack	Margaret J Jack	
18 ADDRESS *(Number, Street, City, State and Zip Code)*	19 TELEPHONE NUMBER *(Include Area Code)*	20. DATE
Hoffmann-La Roche Inc. 340 Kingsland Street Nutley, New Jersey 07110	(201) 235-4692	May 20, 1988

(WARNING: A willfully false statement is a criminal offense U S C Title 18, Sec 1001)

Notice of Claimed Investigational Exemption for a New Drug

Ro 18-0647 - Tetrahydrolipstatin
Oral Administration

May 12, 1988

OVERALL TABLE OF CONTENTS

		VOLUME	PAGE(s)
3.	**Introductory Statement and General Investigational Plan**	1	1-178
3.1	Introduction	1	1
3.2	Previous Human Experience	1	2
	Reference	1	3-167
3.3	Withdrawal from Investigation or Market Information	1	168
3.4	Overall Investigational Plan	1	169-178

References for Overall Investigational Plan are located in:

References	Volume	Page(s)
1-21	4	1-234
22-37	5	1-286

5.	**Investigator's Brochure**	1	179-209
5.1	Introduction	1	181-189
5.2	Chemistry	1	190-191
5.3.1	Pharmacology	1	192-200
5.3.2	Pharmacokinetics	1	201-203
5.3.3	Toxicology	1	204-206
5.4	Clinical Studies - Foreign	1	207-209

Notice of Claimed Investigational Exemption for a New Drug

Ro 18-0647 - Tetrahydrolipstatin
Oral Administration

May 12, 1988

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Investigator	1	246-249
Alan W. Dunton, M.D. Curriculum Vitae		
Monitor	1	246,250-251
Jonathan B. Hauptman, M.D. Curriculum Vitae		
7. Chemistry, Manufacturing and Control Information	2	1-227
7.a Drug Substance	2	1-91
7.b Drug Product	2	92-173
20 mg/mL Solution	2	92-132
200 mg/mL Solution	2	133-173
7.c Placebo	2	174-190
7.d Labeling	2	191-225
7.e Environmental Analysis	2	226-227

Notice of Claimed Investigational Exemption for a New Drug

Ro 18-0647 - Tetrahydrolipstatin
Oral Administration

May 12, 1988

OVERALL TABLE OF CONTENTS

	VOLUME	PAGE(s)
8. Preclinical Pharmacology and Toxicology	3	1-177
8.1 Pharmacology Summary	3	1-159
8.2 Toxicology Summary	3	160-174
8.3 Biopharmaceutical Summary	3	175-177
References for Preclinical Summaries are located in:		

Summary	Reference	Volume	Page(s)
Pharmacology	1-18	6	1-380
Pharmacology	19-54	7	1-362
Toxicology	1-7	8	1-392
Biopharmaceutics	1	8	393-416

9. Previous Human Experience	3	178-179
9.1 Summary	3	178-179
Reference for Previous Human Experience Summary is located in Volume 1, Pages 3-168		
References	4-8	ALL
Clinical References 1-21	4	ALL
Clinical References 22-37	5	ALL
Pharmacology References 1-18	6	ALL
Pharmacology References 19-54	7	ALL
Toxicology References 1-7	8	1-392
Biopharmaceutics Reference 1	8	393-416

Notice of Claimed Investigational Exemption for a New Drug

Ro 18-0647 - Tetrahydrolipstatin
Oral Administration

May 12, 1988

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Notice of Claimed Investigational Exemption for a New Drug

Ro 18-0647 - Tetrahydrolipstatin
Oral Administration

May 12, 1988

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	Monitor	246,250-251
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6

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-766

DEC 2 1996

Hoffmann-LaRoche Inc.
Attention: Ms. Margaret J. Jack
Program Director
340 Kingsland Street
Nutley, NJ 07110

Dear Ms. Jack:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Xenical (orlistat) Capsules, 120 mg
Therapeutic Classification:	To be determined before the filing date
Date of Application:	November 26, 1996
Date of Receipt:	November 27, 1996
Our Reference Number:	NDA 20-766

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on January 26, 1997, in accordance with 21 CFR 314.101(a).

Should you have any questions concerning this NDA, please contact Maureen Hess, R.D., Consumer Safety Officer, at (301) 443-3490.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely yours,

Enid Galliers
Chief, Project Management Staff
Division of Metabolic and Endocrine
Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

RECEIVED
DEC - 9 1996
DRUG REGULATORY AFFAIRS

HLR #1996-2378

Department of Health and Human Services
Food and Drug Administration

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

Title 21, Code of Federal Regulations, Parts 314 & 601.

FOR FDA USE ONLY

Application Number

APPLICANT INFORMATION

Name of Applicant	Date of Submission
Hoffmann-La Roche Inc.	November 26, 1996
Telephone Number (Include Area Code)	**Facsimile (FAX) Number (Include Area Code)**
(201) 812-3719	(201) 812-3700/3554

Applicant Address (Number, Street, State, Country, and Zip Code o Mail Code):

340 Kingsland Street
Nutley, NJ 07110

Authorized U.S. Agent, name & Address (Number, Street, State, and Zip Code telephone & FAX Number) if applicable

Margaret J. Jack
Hoffmann-La Roche Inc.
340 Kingsland Street
Nutley, NJ 07110
(201) 812-3719 fax (201) 812-3700/3554

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE NUMBER (if previously issued) 20-766

PRODUCT DESCRIPTION

Established Name (e.g., Proper name, USP/USAN name)	Proprietary Name (trade name) if any
Orlistat, Tetrahydrolipstatin	XENICAL®

Chemical/Biochemical Name (If any) (S)-2-formylamino-4-methyl-pentanoic acid (S)-1-[[(2S, 3S)-3-hexyl-4-oxo-2-oxetanyl]methyl]-dodecyl ester.

Code Name (if any): Ro 18-0647

Dosage Form:	Strengths:	Route of Administration:
capsules	120 mg	oral

Proposed Indications for Use:
Treatment of obesity.

APPLICATION INFORMATION

APPLICATION TYPE (check one)

☒ **NEW DRUG APPLICATION** (21 CFR 314.50) ☐ **ABBREVIATED APPLICATION** (ANDA, AADA, 21 CFR 314.94)

☐ **BIOLOGIC APPLICATION** (21 CFR part 601)

IF A NDA, IDENTIFY THE APPROPRIATE TYPE ☒ **505 (b)(1)** ☐ **505 (b)(2)** ☐ **507**

IF AN ANDA, or AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug **Holder of Approved Application**

TYPE OF SUBMISSION (check one)

☒ **Original Application** ☐ **Amendment to a Pending Application** ☐ **Resubmission**

☐ **Presubmission** ☐ **Notification** ☐ **Establishment Description Supplement**

☐ **SUPAC Supplement** ☐ **Efficacy Supplement** ☐ **Labeling Supplement** ☐ **Chemistry, Manufacturing & Controls Supplement**

REASON FOR SUBMISSION
Submission of original, new drug application for XENICAL.

PROPOSED MARKETING STATUS (Check one) ☒ **Prescription Product (Rx)** ☐ **Over-The-Counter Product (OTC)**

Number of Volume Submitted: 672	This application is ☐ Paper ☒ Paper and Electronic

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs ,510(k)s, IDEs, BMFs and DMFs referenced in the current application)

PLEASE SEE VOLUME(S)
FOR COMPLETE DATA

[redacted]

This submission contains the following items (check all that apply)	
X	1. Index
X	2. Labeling (check one) ☒ Draft Labeling ☐ Final Printed Labeling
X	3. Summary (e.g. 21 CFR 314.50 (c))
X	4. Chemistry section
X	A. Chemistry, manufacturing and control information (e.g. 21 CFR 314.50 (d)(1))
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
X	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (1))
X	5. Nonclinical pharmacology and toxicology section (e.g 21 CFR 314.50 (d) (2))
X	6. Human pharmacokinetics and bioavailability section (e.g 21 CFR 314.50 (d) (3))
	7. Clinical Microbiology (e.g 21 CFR 314.50 (d) (4))
X	8. Clinical data section (e.g 21 CFR 314.50 (d) (5))
	9. Safety update report (e.g 21 CFR 314.50 (d) (5) (vi) (b))
X	10. Statistical section (e.g 21 CFR 314.50 (d) (6))
X	11. Case report tabulations (e.g 21 CFR 314.50 (f) (1))
X	12. Case report forms (e.g 21 CFR 314.50 (f) (1))
X	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
X	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
	15. Establishment description (21 CFR Part 600, if applicable)
X	16. Debarment certification
X	17. Field copy certification
X	18. User Fee Cover Sheet (Form FDA 3397)
	19. Other (Specify)

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to, the following:

1. Good manufacturing practice regulations in 21 CFR 210, 211, 606 and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610 and/or 809.
4. In the case of a prescription drug product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72 and 601.12.
6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the controlled substance act, I agree not to market the product until the drug enforcement administration makes a final scheduling decision.

The data and information in this submission have been reviewed and are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

Signature of responsible official or agent	Typed name and title	Date
Margaret J Jack	Margaret J. Jack, Program Director HLR No. 1996-2263	11/26/96

Roche **Roche Pharmaceuticals**
A Member of the Roche Group

Hoffmann-La Roche Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199

Direct Dial (201) 812-3719
Fax (201) 812-3700/3554

November 26, 1996

Food and Drug Administration
Division of Metabolism and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research
ATTN: DOCUMENT CONTROL ROOM, 14B-19
5600 Fishers Lane
Rockville, MD 20857-1706

Ladies and Gentlemen:

Re: NDA 20-766
XENICAL® (orlistat) capsules
Original New Drug Application

In accordance with 21CFR Part 314.50, Hoffmann-La Roche Inc. herewith is submitting an original New Drug Application (NDA 20-766) for XENICAL® (orlistat) 120 mg capsules, indicated for long-term weight control (weight loss, weight maintenance and prevention of weight regain) in conjunction with a mildly hypocaloric diet. The data included in this NDA demonstrates that XENICAL is effective for the long-term treatment of obese and overweight patients and for the improvement of risk factors associated with obesity. Orlistat has been the subject of IND 31,617 sponsored by Hoffmann-La Roche Inc., Nutley, NJ.

XENICAL is a potent, specific and long acting inhibitor of lipases. It exerts its therapeutic activity in the lumen of the stomach and small intestine by forming a covalent bond with the active serine site of gastric and pancreatic lipases. The inactivated enzymes are thus unavailable to hydrolyze dietary fat in the form of triglycerides into absorbable free fatty acids and monoglycerides. As undigested triglycerides are not absorbed, the resulting caloric deficit has a positive effect on weight control. Systemic absorption of the drug is therefore not needed for activity.

The information submitted in this NDA in support of the safety and efficacy of XENICAL has been derived from studies conducted under the above-mentioned IND and from non-US preclinical and non-IND clinical studies conducted under the auspices of F. Hoffmann-La Roche Ltd., Basel Switzerland.

The Phase 3 clinical program for XENICAL consisted of 7 multi-center, randomized, double blind, placebo-controlled trials of which four studies were 2 years of active treatment and three studies were 1 year of active treatment. One of the 1 year studies was conducted in obese patients with non-insulin dependent diabetes mellitus maintained on oral hypoglycemic agents and another

study was conducted in obese patients who lost 8% of their weight by diet alone in the 6 months prior to receiving 1 year of XENICAL therapy. The safety and efficacy data bases for the XENICAL Phase 3 clinical program are large consisting of over 2000 patients completing one year of XENICAL therapy and approximately 900 patients completing two years of XENICAL therapy. These seven studies are complete and all safety and efficacy analyses are included in this NDA.

The Phase 2 program consists of eleven double-blind, placebo controlled studies of which 7 studies were conducted in obese patients and four studies were conducted in mostly non-obese hypercholesterolemic patients. These studies were up to 6 months in duration. There were over 800 XENICAL treated patients in the Phase 2 program. All the data and analyses for these studies are included in this NDA.

The Phase 1 program consisted of 66 studies in which over 1,000 subjects received orlistat. These studies were up to 6 weeks in duration, and all these studies are included in the NDA.

The integrated safety summary includes all the safety data from the total clinical development program (Phase 1, 2 and 3) with the exception of one Phase 1 study which was completed after the integrated safety data base was closed. A complete study report for this study is in the NDA.

As per the sponsor's previous agreement with the Agency, Section 11 case report tabulations and summaries are not included in this submission due to the size of this section (approximately 1,300 volumes). These data can be retrieved on the CANDA for Phase 3 patients and the sponsor has agreed to provide any part of Section 11 on an as needed basis within 48 to 72 hours of the request.

The CANDA will be delivered to the Agency during the week of December 16, 1996 as per the sponsor's agreement with the medical reviewer, Dr. Eric Colman. The CANDA will include Phase 3 safety and efficacy data only, case report forms for death and dropouts due to adverse events for Phase 3, all clinical summaries, the final study reports for the seven Phase 3 studies and the proposed draft labeling for XENICAL.

As previously mentioned, all Phase 1, 2, and 3 clinical trials have been completed, and the data are in NDA 20-766. There is one ongoing Phase 3b trial being conducted in the UK with 50 hypercholesterolemic patients randomized to 120 mg t.i.d. XENICAL or placebo. The data from this trial are not available at this time.

As per the sponsor's previous agreement with the Agency, the 9-month data from a toxicology study conducted in rats maintained on a high fat/low calcium diet is not included in NDA 20-766. The data following the 3-month and 6-month interim sacrifices for this study are included in Section 5 and the 9 month data will be provided in the 4-month safety update.

A field copy containing a completed Form 3439, Section 3 (Application Summary) and Section 4 (chemistry, manufacturing and controls) of this NDA is being submitted simultaneously to the New Brunswick, NJ, District Office of the FDA. The undersigned hereby certifies that the copy submitted to the District Office is a true copy of that which is submitted to the Division of Metabolism and Endocrine Drug Products.

This submission consists of an archival copy (672 volumes) and required number of review copies. NDA 20-766 is organized as follows:

Section Number:	Volume No.
Section 1 - Index	**1**
Section 2 - Labeling	**2**
Section 3 - Application Summary	**3-4**
Section 4 - Chemistry, Manufacturing and Controls	**5-18**
Section 5 - Nonclinical Pharmacology and Toxicology	**19-120**
Section 6 - Human Pharmacokinetics and Bioavailability	**121-151**
Section 8/10 - Clinical and Statistical Data	**152-467**
Background and Overview Summary	152
Risk/Benefit Assessment	152
Drug Abuse and Overdose	152
Clinical Pharmacology Summary, Table of Studies, References	153
Phase II Controlled Trials - Obesity & Lipid Lowering Studies	236-277
Phase III Controlled Clinical Trials	278-452
Additional Efficacy and Safety Analyses of Phase III Data	453
Additional Safety Assessments by Consultants	454-456
Integrated Summary of Efficacy	457-460
Integrated Summary of Safety	461-463
Other references Cited in Section 8/10	464-465
Curriculum Vitae of Investigators	466-467
Section 11 Case Report Tabulations not provided	
Section 12 Case Report Forms, Deaths and Dropouts	**468-672**

Two desk copies of the Index (Section 1) for the entire NDA, labeling (Section 2) and the Application Summary (Section 3) are being provided directly to Ms. Maureen Hess, CSO in the Division of Metabolism and Endocrine Drug Products.

We understand that this New Drug Application and all information contained herein, unless otherwise made public by Hoffmann-La Roche Inc. is CONFIDENTIAL and will remain so subsequent to approval of the NDA for this drug. If for any reason Food and Drug Administration officials should at any time feel that disclosure of any of the materials contained in this NDA should be made public, Hoffmann-La Roche Inc. will be consulted first on the issue of disclosure.

As per Serial Submission No. 138 dated September 6, 1996 to IND 31,617, the sponsor is again requesting priority review of this NDA. The rational for priority review was provided in Serial Submission No. 138.

Please contact the undersigned at (201) 812-3719 by telephone or via fax at (201) 812 3700/3554 for any additional clinical or preclinical information concerning NDA 20-766 or IND 31,617. Any issues related to the chemistry, manufacturing, and controls of this compound may be addressed to Ms. Virginia A. Pate at (201) 812-3550.

Sincerely,

HOFFMANN-LA ROCHE INC.

Margaret J Jack

Ms. Margaret J. Jack
Program Director
Drug Regulatory Affairs

Attachments
MJJ:LS/jw
HLR No. 1996-2263
Desk Copies: Ms. Maureen Hess

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. *0910-0297*
Expiration Date: *November 30, 1996*

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form.

1. APPLICANT'S NAME AND ADDRESS

Hoffmann-La Roche Inc.
340 Kingsland Street
Nutley, NJ 07110

2. USER FEE BILLING NAME, ADDRESS, AND CONTACT

Margaret J. Jack
Program Director
Hoffmann-La Roche Inc.
340 Kingsland Street
Nutley, NJ 07110

3. TELEPHONE NUMBER (*Include Area Code*)
(201) 812-3719

4. PRODUCT NAME
Xenical, Orlistat, Ro 18-0647, Tetrahydrolipstatin

5. DOES THIS APPLICATION CONTAIN CLINICAL DATA? ☒ YES ☐ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT. STOP AND SIGN THIS FORM.

6. USER FEE I.D. NUMBER
33 299

7. LICENSE NUMBER/NDA NUMBER
20-766

8. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED BEFORE 9/1/92

☐ THE APPLICATION IS SUBMITTED UNDER 505(b)(2) *(See reverse side before checking box.)*

☐ AN INSULIN PRODUCT SUBMITTED UNDER 506

FOR BIOLOGICAL PRODUCTS ONLY

☐ WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION

☐ A CRUDE ALLERGENIC EXTRACT PRODUCT

☐ BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92

☐ AN "IN VITRO" DIAGNOSTIC BIOLOGIC PRODUCT LICENSED UNDER 351 OF THE PHS ACT

9. a. HAS THIS APPLICATION QUALIFIED FOR A SMALL BUSINESS EXCEPTION? ☐ YES ☒ NO *(See reverse if answered YES)*

b. HAS A WAIVER OF APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES ☒ NO *(See reverse if answered YES)*

This completed form must be signed and accompany each new drug or biologic product, original or supplement

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Margaret J. Jack Margaret J Jack	Program Director Drug Regulatory Affairs	November 26, 1996

FORM FDA 3397 (12/93)

Roche Pharmaceuticals
A Member of the Roche Group

Hoffmann-La Roche Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199

Direct Dial (201) 812-3719
Fax (201) 812-3700/3554

November 26, 1996

Food and Drug Administration
P.O. Box 7777-W7745
Philadelphia, PA 19175-7745

Attn: Wholesale Lockbox 1993490

Ladies and Gentlemen:

Re: **HUMAN DRUG APPLICATION FEE - NDA 20-766**
Xenical® (orlistat, tetrahydrolipstatin)

Enclosed please find a check in the amount of $116,500.00 made payable to the U.S. Food and Drug Administration. This payment represents the initial installment of the user fee required for our Original New Drug Application for Xenical® (orlistat, tetrahydrolipstatin) dated November 26, 1996.

If you have any questions, please do not hesitate to contact the undersigned.

Sincerely,

HOFFMANN-LA ROCHE INC.

Margaret J Jack

Margaret J. Jack
Program Director
Drug Regulatory Affairs

MJJ/LS:jw
Enclosure: Check #01210990
HLR No. 1996-2272

HOFFMANN-LA ROCHE INC.
NUTLEY, NEW JERSEY 07110

CHECK NO. 01210990
VENDOR 111554-10

VOUCHER NUMBER	INVOICE NUMBER	PURCHASE ORDER	INVOICE DATE	AMOUNT	DISCOUNT	NET
937383	APJ-316		11-05-96	116,500.00	.00	116,500.00
TOTALS				116,500.00	.00	116,500.00

:031100209:38827273< 01210990 111554-10116,500.00US FOOD & DRUG ADM

HOFFMANN-LA ROCHE INC.
NUTLEY, NEW JERSEY 07110

62-20
311

PAY **********

DATE 11/15/96

CHECK NO. 01210990

NET AMOUNT ****116,500.00

ONE HUNDRED SIXTEEN THOUSAND FIVE HUNDRED DOLLARS AND 00 CENTS

TO THE ORDER OF US FOOD & DRUG ADMINISTRATION
PO BOX 360909
PITTSBURGH PA 15251-6909

Citibank (Delaware)
One Penn's Way
New Castle, De 19720

William L. Hamm

TREASURER

⑈01210990⑈ ⑆031100209⑆ 38827273⑈

Roche **Roche Pharmaceuticals**
A Member of the Roche Group

Hoffmann-La Roche Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199

Direct Dial (201) 812-3550
Fax (201) 812-3700/3554

November 26, 1996

Ms. Regina Brown
Preapproval Program Director
Food and Drug Administration
120 North Central Drive
North Brunswick, NJ 08902

Dear Ms. Brown:

RE: **Xenical® (orlistat, tetrahydrolipstatin)**
Original New Drug Application 20-766

In accord with 21 CFR 314.50 (k)(3), we hereby submit a field copy of the cover letter, the completed Form FDA 3439, Section 3 (Application Summary) and Sections 4A and 4B (CMC - Drug Substance and Drug Product) for the referenced New Drug Application. The undersigned hereby certifies that this copy is a true copy of that submitted to the Division of Metabolism and Endocrine Drug Products.

We consider the information contained in this submission to be CONFIDENTIAL and not to be disclosed to any person outside the Food and Drug Administration without prior notification and written consent of Hoffmann-La Roche Inc.

Sincerely,

HOFFMANN-LA ROCHE INC.

Virginia A. Pate

Virginia A. Pate
Program Manager
Drug Regulatory Affairs

MJJ/LS:jw
HLR No. 1996-2273

DEBARMENT CERTIFICATION

Hoffmann-La Roche Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under 21 U.S.C. 335a (a) and (b), in connection with this application.

PATENT INFORMATION[1]

1.	Active Ingredient(s):	Orlistat
2.	Strength(s):	120 mg
3.	Trade Name:	Xenical®
4.	Dosage form and Route of Administration	capsule, oral
5.	Application Firm Name:	Hoffmann-La Roche Inc.
6.	NDA Number:	20-766
7.	First Approval Date:	None[2]
8.	Exclusivity:	Subject to patent rights, first ANDA can be submitted five years from date of pending NDA approval.
9.	Patent Information:	
	Patent Number and Expiration date:	4,598,089 6/18/2004[3]
	Type of Patent:	Drug
	Patent Owner:	Hoffmann-La Roche Inc.

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[1] While this submission was prepared in good faith, no warranty or guarantee is made regarding the accuracy or completeness of the information contained therein.

[2] Since the New Drug Application has not yet been approved, this submission is considered as constituting trade secrets or commercial or financial information which is privileged or confidential within the meaning of the Freedom of Information Act (5 USC 552). It is requested that this submission not be published until the New Drug Application has been approved.

[3] Subject to patent term extension provisions for 35 USC § 156 et seq.

CONFIDENTIAL INFORMATION

Since the New Drug Application has not yet been approved, this submission is considered as constituting trade secrets or commercial or financial information which is privileged or confidential within the meaning of the Freedom of Information Act (5 USC 552). It is requested that this submission not be published until the New Drug Application has been approved.

1

Xenical IND
31,617

Communication	Type of Communication	Date of Communication
Orlistat Oral Solution for Treatment of Obesity and Associated Hyperlipidemias	IND Original	5/12/88
FDA acknowledged receipt of 5/12/88 of Original IND for Tetrahydrolipstatin, on 5/13/88. Assigned IND number 31,617.	FDA Letter	5/13/88
FDA called 6/3/88, stating FDA could not review original IND in 30 days and needed more time.	File Note	6/7/88
Information Amendment: Pharmacology/Toxicology - Toxicology Reports -	IND Amendment-Letter/Form/Index	6/8/88
Several calls 6/16-24 to FDA concerning status of review of the IND.	File Note	7/1/88
FDA requested additional information on toxicology data	FDA Letter	7/22/88
FDA request for information in connection with the rat toxicity study submitted 6/8/88. Requested triglyceride determinations, plasma drug concentrations and hepatic triglyceride concentration and serum lipoprotein lipase values in rat.	FDA Letter	7/22/88
Information Amendment: Pharmacology/Toxicology - Toxicology Report. Response to FDA Request - Provided information.	IND Amendment-Letter/Form/Index	7/28/88
Protocol Amendment: Change in Protocol - New Investigator	IND Amendment-Letter/Form/Index	9/26/88
Information Amendment: Pharmacology/Toxicology - Toxicology Reports.	IND Amendment-Letter/Form/Index	10/6/88
Protocol Amendment: New Protocol - Provided a copy of Protocol Amendment.	IND Amendment-Letter/Form/Index	11/21/88
Protocol Amendment: Change in Protocol - Information Amendment: Chemistry, Manufacturing and Controls	IND Amendment-Letter/Form/Index	1/9/89
Protocol Amendment: Change in Protocol and New Investigator.	IND Amendment-Letter/Form/Index	2/8/89
Response to FDA Request for Information - Provided preclinical, clinical and technical information requested in two FDA letters dated 7/22/88.	IND Other-Letter/Form/Index	2/23/89
Protocol Amendment: New Protocol and New Investigator. Information Amendment: Pharmacology/Toxicology - Toxicology Reports.	IND Amendment-Letter/Form/Index	3/13/89
Telephone call 4/20/89 from FDA requesting that we speak to FDA prior to initiating carcinogenicity studies.	File Note	4/20/89
Protocol Amendment: New Protocol. New Investigator.	IND Amendment-Letter/Form/Index	5/5/89
IND Safety Report: Initial Written Report - Investigator.	IND Other-Letter/Form/Index	5/10/89
Telephone call to FDAI 5/18/89. Informed FDA that prior to initiating studies we would discuss study designs with FDA.	File Note	5/19/89
Telephone call to FDA 5/20/89, concerning the Initial 10-Day Safety Report submitted 5/10/89.	File Note	5/24/89
Protocol Amendment: New Protocol and New Investigator.	IND Amendment-Letter/Form/Index	6/1/89

Communication	Type of Communication	Date of Communication
Telephone call from FDA 6/5/89, regarding recent inquiries into FDA's requirements for inclusion of women of childbeing potential in Phase II and III studies.	File Note	6/12/89
Annual Report covering the reporting period of 5/12/88 thru 5/11/89.	IND Annual Report-Letter/Form/Index	7/11/89
Protocol Amendment: New Protocols and New Investigator. Information Amendment: Chemistry, Manufacturing and Controls.	IND Amendment-Letter/Form/Index	8/4/89
Response to FDA Request for Information - Provided response to FDA letter dated 7/14/89 requesting additional information on data submitted 1/9/89 and 2/23/89.	IND Other-Letter/Form/Index	9/14/89
Protocol Amendment: New Protocol and New Investigator. Information Amendment: Pharmacology/Toxicology - Toxicology Reports. Information Amendment: Chemistry, Manufacturing and Controls.	IND Amendment-Letter/Form/Index	10/10/89
Protocol Amendment: New Protocol and New Investigator. Information Amendment: Chemistry, Manufacturing and Controls - Revised specifications and directions for testing. Response to FDA Request for Information: Composition and specifications and directions for testing.	IND Amendment-Letter/Form/Index	10/20/89
Protocol Amendment: New Protocol and New Investigator.	IND Amendment-Letter/Form/Index	11/14/89
Protocol Amendment: New Protocols and New Investigators. IND Safety Report.	IND Amendment-Letter/Form/Index	12/20/89
Protocol Amendment: Change in Protocols.	IND Amendment-Letter/Form/Index	1/29/90
Protocol Amendment: Change in Protocols. Information Amendment: Pharmacology/Toxicology - Toxicology Report.	IND Amendment-Letter/Form/Index	2/20/90
Protocol Amendment: Change in Protocol.	IND Amendment-Letter/Form/Index	3/20/90
FDA reviewed Annual Report dated 7/11/89 and has requested that carotene and vitamins E and A be monitored in future studies and that preliminary data from certain clinical pharmacology studies be reviewed by FDA.	FDA Letter	4/3/90
Provided a desk copy of the follow-up IND safety report for patient. Follow-up was submitted in Serial Submission No. 019 dated 12/20/89. The initial safety report was submitted 5/10/89 in Serial Submission No. 011.	IND Other-Letter/Form/Index	6/22/90
Telephone call 6/15/90 from FDA with several questions concerning the progress of the clinical trials under this IND.	File Note	6/22/90
Protocol Amendment: Change in Protocol.	IND Amendment-Letter/Form/Index	6/28/90
Annual Report covering the reporting period of 5/12/89 thru 5/11/90.	IND Annual Report-Letter/Form/Index	7/9/90
Protocol Amendment: New Protocol and New Investigator. Information Amendment: Chemistry, Manufacturing and Controls.	IND Amendment-Letter/Form/Index	7/20/90

Communication	Type of Communication	Date of Communication
Telephone call to FDA 8/17/90 to ascertain whether the Agency has a preference for units to be used in clinical study reports for THL--conventional units vs. SI units. FDA checked with several medical reviewers who all preferred conventional units.	File Note	8/17/90
Protocol Amendment: New Protocols.	IND Amendment-Letter/Form/Index	8/27/90
Protocol Amendment: Change in Protocols and New Investigators.	IND Amendment-Letter/Form/Index	10/2/90
Protocol Amendment: New Protocol. Information Amendment: Chemistry, Manufacturing and Controls - Revised specifications and directions for testing and retesting of capsules.	IND Amendment-Letter/Form/Index	11/8/90
Protocol Amendment: New Protocol and New Investigator. Information Amendment: Chemistry, Manufacturing and Controls - Drug Product: Controlled release formulations.	IND Amendment-Letter/Form/Index	1/23/91
IND Safety Report: Initial Written Report - Foreign ADE- Non-IND Study	IND Other-Letter/Form/Index	1/24/91
Change of Protocols and New Investigators. Information Amendment: Chemistry, Manufacturing and Controls -- Packaging procedures, stability and specifications and directions for testing of packaging materials.	IND Amendment-Letter/Form/Index	2/1/91
IND Safety Report: Initial Written Report - Foreign ADE - Non-IND Study	IND Other-Letter/Form/Index	2/15/91
Telephone calls 2/14 and 2/21/91 from FDA to establish a March date for a meeting to review the THL clinical program. Medical Reviewer to complete his review of currently available information.	File Note	2/20/91
Protocol Amendment: Change in Protocols.	IND Amendment-Letter/Form/Index	4/2/91
Telephone call 5/7/91 from FDA to schedule a meeting at FDA to review the THL development status.	File Note	5/13/91
FDA comments and recommendations on clinical protocols and 1990 annual report. Additional requests included, efficacy and pharmacokinetic data, preclinical and clinical absorption data, and request to review preclinical carcinogenicity protocol prior to initiation.	FDA Letter	5/15/91
Telephone call 5/29/91 to FDA to discuss preliminary agenda for the 7/91 meeting with FDA.	File Note	5/31/91
General Correspondence: Pre-meeting Information including attendees, agenda and background material relevant to data being presented at the meeting. Meeting with FDA scheduled for 7/19/91 to update FDA on the development status.	IND Other-Letter/Form/Index	6/26/91
IND Safety Report: Initial Written Report - Foreign ADE - Non-US IND Study.	IND Other-Letter/Form/Index	7/8/91
Annual Report covering the reporting period of 5/12/90 thru 5/11/91.	IND Annual Report-Letter/Form/Index	7/12/91

Communication	Type of Communication	Date of Communication
IND Safety Report: Initial Written Report.	IND Other-Letter/Form/Index	7/18/91
Response to FDA Request for Information - Provided response to FDA letter dated 5/15/91, which requested additional information on four previous submissions and submission of additional efficacy, safety, and pharmacokinetic data.	IND Other-Letter/Form/Index	8/16/91
Minutes of FDA Meeting of 7/19/91 concerning the development status and follow-up discussions.	File Note	8/21/91
General Correspondence: Minutes of Meeting with FDA held on 7/19/91. The purpose of the meeting was to update FDA on the development status.	IND Other-Letter/Form/Index	8/27/91
Information Amendment: Pharmacology/Toxicology - Preclinical Toxicology Reports.	IND Amendment-Letter/Form/Index	9/5/91
Protocol Amendment: Change in Protocols	IND Amendment-Letter/Form/Index	9/24/91
FDA minutes of meeting with Roche held 7/19/91 to review status of THL preclinical and clinical studies.	-FDA Letter	9/27/91
Protocol Amendment: New Protocol and New Investigator.	IND Amendment-Letter/Form/Index	11/19/91
Response to FDA Request for Information - FDA letter, 5/15/91. Submitted rat and mouse dosing range-finding studies data and draft carcinogenicity protocols for review and comment before initiation of studies. Information Amendment: Pharmacology/Toxicology - Toxicology Final Study Report.	IND Amendment-Letter/Form/Index	11/21/91
Information Amendment: Chemistry and Toxicology - Additional information requested concerning the analytical methodologies used to determine the preclinical and clinical plasma concentrations. Chemistry Report and Bioanalytical Report.	IND Amendment-Letter/Form/Index	12/4/91
Information Amendment: Toxicology - Proposed carcinogenicity protocol for tetrahydrolipstatin in rat included in S#042, dated 11/21/91.	IND Amendment-Letter/Form/Index	12/20/91
Protocol Amendment: Change in Protocol. Information Amendment: Toxicology Report.	IND Amendment-Letter/Form/Index	1/7/92
FDA confirmed dose levels for rat carcinogenicity study and requested plasma concentrations during carcinogenicity study and submission of plasma concentrations for one-year rat study.	FDA Letter	1/9/92
Information Amendment: Clinical - Four pharmacokinetic drug interaction studies and an excretion balance/pharmacokinetic study in man.	IND Amendment-Letter/Form/Index	1/31/92
FDA comments and recommendations regarding submission dated 9/5/91 (S-040).	-File Note	2/10/92
FDA comments and recommendations regarding the drug substance and synthesis information provided in submissions dated 7/20/90, 11/8/90, 1/23/91, and 2/1/91.	-FDA Letter	2/18/92
Information Amendment: Clinical - Six final study reports for Phase I clinical studies.	IND Amendment-Letter/Form/Index	2/20/92

Communication	Type of Communication	Date of Communication
Telephone conversation 3/5/98 with FDA concerning the dose selection for the mouse carcinogenicity study.	File Note	3/6/92
Protocol Amendment: New Protocol. Information Amendment: Clinical - Preliminary Study Reports - U.S. Phase 2 Study. Non-U.S. Phase 2 Study. Request for End-of Phase 2 Meeting.	IND Amendment-Letter/Form/Index	3/6/92
FDA confirmed the End of Phase 2 meeting between Roche and FDA for 4/30/92.	File Note	4/14/92
General Correspondence: Pre-meeting information including attendees, agenda and proposed clinical plan. Requested an End-of-Phase 2 meeting in submission dated 3/6/92, to discuss the future development of orlistat for treatment of obesity.	IND Other-Letter/Form/Index	4/24/92
Follow-up conversation 6/4/92 with FDA concerning the End of Phase 2 meeting held 4/30/92.	File Note	6/8/92
General Correspondence: Minutes of the End-of-Phase 2 Meeting with FDA, 4/30/92. The purpose of the meeting was to obtain FDA's agreement on proceeding with the long term Phase 3 clinical program, and to obtain FDA concurrence on the approvability of the targeted indication based on the overall Phase 3 clinical plan.	IND Other-Letter/Form/Index	6/22/92
Annual Report covering the reporting period of 5/12/91 thru 5/11/92.	IND Annual Report-Letter/Form/Index	7/12/92
Protocol Amendment: New Protocol and Follow-up to End-of-Phase 2 meeting held on 4/30/92. General Correspondence: Requested a meeting to discuss the revised, proposed Phase 3 clinical plan in support of a long term weight control indication.	IND Amendment-Letter/Form/Index	7/17/92
FDA has completed review of our 2/20/92 submission which contained six final reports for eight Phase 1 clinical studies. Requested additional information concerning these studies.	File Note	7/20/92
Follow-up communication with FDA 7/17/92 concerning End of Phase 2 meeting. Requested copy of FDA issued minutes and if there was consultation with Neuropharmacology Division concerning approvability of the indication of long term weight control vs. weight loss.	File Note	8/4/92
Information Amendment: Clinical - Final Study Reports.	IND Amendment-Letter/Form/Index	8/18/92
Discussion with FDA 8/13/92 regarding follow-up to End of Phase 2 meeting, discussion with Neuropharmacology Division, and the previously proposed Phase 3 study.	File Note	8/21/92
Meeting scheduled for 10/14/92 to discuss revised targeted indication and the revised Phase 3 clinical plan for orlistat based on input received at the 4/30/92 End of Phase 2 meeting. Phase 3 protocol is still being reviewed.	File Note	9/8/92

Communication	Type of Communication	Date of Communication
Roche received FDA paper, "Obesity, How to Evaluate Drugs Intended to Assist in Weight Loss".	File Note	9/9/92
Protocol Amendment: New Investigators. Information Amendment: Clinical/Chemistry - Change in synthesis (dihydropyrone synthesis), Drug substance manufacture, Dosage Form.	IND Amendment-Letter/Form/Index	9/28/92
Protocol Amendment: New Protocol, New Investigator. Information Amendment: Chemistry, Manufacturing and Controls: Drug Substance - Dosage Form - 120 mg capsules.	IND Amendment-Letter/Form/Index	9/29/92
FAX - FDA review of Phase 3 Protocol.	FDA Letter	10/28/92
Information Amendment: Chemistry, Manufacturing and Controls - Dosage Form - 60 mg capsules pelletted formulation and their matching placebos. These capsules will be used in the Phase 3 clinical program. Provided side by side comparisons of certain formulation parameters.	IND Amendment-Letter/Form/Index	10/30/92
Information Amendment: Pharmacology/Toxicology - Four volumes of preclinical reports, including toxicology, pharmacology and preclinical drug metabolism-pharmacokinetic reports.	IND Amendment-Letter/Form/Index	10/30/92
General Correspondence - Pre-meeting information including attendees, agenda and revised Phase 3 clinical plan. Meeting scheduled for 11/10/92.	IND Other-Letter/Form/Index	10/30/92
General Correspondence: Response to fax from FDA concerning review of Protocol. A response to these inquiries would require consultation with several technical disciplines in both the US and Europe. Requested postponement of the follow-up to the end-of-Phase 2 meeting scheduled for 11/10/92, until a complete response to FDA's inquiries concerning Protocol is submitted and reviewed by FDA.	IND Other-Letter/Form/Index	11/5/92
Follow-up communication 9/16/92 with FDA concerning differences between Metabolism and Endocrine Drug Products Division and Neuropharmacology division's requirements for approval of obesity products.	File Note	11/9/92
FDA issued Minutes of the End of Phase 2 Meeting held 4/30/92.	FDA Letter	11/12/92
Protocol Amendment: New Investigators - Protocol.	IND Amendment-Letter/Form/Index	11/18/92
Information Amendment: Chemistry - Comparison of impurity profile. Toxicology summarized the toxicology studies completed to-date in rat, mouse and dog, respectively. Clinical Studies include a tabulation of the Phase 1 and 2 clinical studies conducted under this IND and the synthesis and polymorphic form of the study.	IND Amendment-Letter/Form/Index	12/15/92

Communication	Type of Communication	Date of Communication
Petitioned FDA to resolve differences in approval criteria for obesity drug therapies between divisions.	IND Other-Letter/Form/Index	12/16/92
IND Safety Report: Initial Written Report - Foreign ADE - Non-US IND Study.	IND Other-Letter/Form/Index	1/14/93
Protocol Amendment: New Investigators - Change in Investigator Data.	IND Amendment-Letter/Form/Index	1/27/93
Telephone call 2/1/93 concerning status of Roche's request for FDA to resolve approval requirements for obesity products between the two review divisions.	File Note	2/1/93
Response to FDA Request for Information - Provided response to facsimile dated 10/28/92, received 11/3/92, from FDA concerning review of Protocol.	IND Other-Letter/Form/Index	2/9/93
Protocol Amendment: New Protocol and New Investigators.	IND Amendment-Letter/Form/Index	2/12/93
Telephone call 2/16/93 concerning our petition of 12/16/92. FDA divisions responsible for approval of obesity therapies will meet to discuss approval criteria for these therapies.	File Note	2/18/93
IND Safety Report: Initial Written Report.	IND Other-Letter/Form/Index	2/24/93
IND Safety Report: Initial Written Report - Foreign ADE - Non-US Study - Investigator.	IND Other-Letter/Form/Index	2/26/93
Protocol Amendment: New Investigators.	IND Amendment-Letter/Form/Index	3/10/93
Information Amendment: Toxicology - Response to FDA Request for Information - Submitted carcinogenicity protocols for review and comment prior to initiation of these studies and the proposed mouse carcinogenicity study.	IND Other-Letter/Form/Index	3/23/93
Telephone call to FDA 4/5/93 regarding our proposal for doses to be used in the mouse carcinogenicity study.	File Note	4/6/93
Telephone call to FDA 4/7/93 regarding FDA recommending doses for planned mouse carcinogenicity study.	File Note	4/8/93
Telephone call to FDA 4/6/93, regarding status of HLR petition requesting FDA to resolve the differences in approval criteria for obesity therapies.	File Note	4/14/93
Several telephone calls regarding proposed doses of orlistat to be administered during conduct of mouse carcinogenicity study.	File Note	4/20/93
Protocol Amendment: New Protocol - New Investigator.	IND Amendment-Letter/Form/Index	4/22/93
Protocol Amendment: New Investigator.	IND Amendment-Letter/Form/Index	4/27/93
FDA had several comments and requests concerning review of pharmacokinetic drug interaction studies and the 14C excretion balance/pharmacokinetic study in man and dose selection/rationale for the mouse carcinogenicity study.	FDA Letter	4/28/93

Communication	Type of Communication	Date of Communication
FDA letter refers to Protocol submitted 7/17/92 and their fax dated 10/28/92. Letter contains biostatistical comments and recommendations regarding the diet, sample size, and statistical analysis.	FDA Letter	5/3/93
Telephone call 4/29/93 to FDA concerning status of the Roche petition requesting resolution of differences in approval criteria for obesity therapies between the two FDA reviewing divisions.	File Note	5/4/93
Information Amendment: Clinical - Submission dated 12/16/92 petitioned Division of Metabolism and Endocrine Drug Products to resolve the apparent differences in approval criteria for obesity therapies which currently exist with Neuropharmacology Division.	IND Amendment-Letter/Form/Index	5/11/93
Protocol Amendment: New Protocol - New Investigator.	IND Amendment-Letter/Form/Index	5/14/93
IND Safety Report: Initial Written Report - Foreign ADE - Non-US IND Study.	IND Other-Letter/Form/Index	5/28/93
Information Amendment: Pharmacology/Toxicology Reports - Toxicology Studies and Pharmacology Studies.	IND Amendment-Letter/Form/Index	6/11/93
Protocol Amendment: New Protocol - New Investigators - Protocol.	IND Amendment-Letter/Form/Index	7/6/93
Annual Report covering the period of 5/92 thru 5/93.	IND Annual Report-Letter/Form/Index	7/12/93
Information Amendment: Clinical Reports. Non-US IND Study - Final Study Reports.	IND Amendment-Letter/Form/Index	7/12/93
Information Amendment: Pharmacology/Toxicology - Preclinical study reports which include data on orlistat's effect on colonic cell proliferation and colonic cell turnover.	IND Amendment-Letter/Form/Index	7/12/93
Telephone calls 7/27 and 8/3/93, from FDA requesting additional information on specific toxicology studies--in rat and dog, cell proliferation study and carcinogenicity studies.	File Note	8/6/93
Telephone call 8/11/93 to FDA concerning the cell proliferation study in rat.	File Note	8/20/93
IND Safety Report: Initial Written Report.	IND Other-Letter/Form/Index	9/17/93
Response to FDA Request for Information - FDA letter dated 5/3/93 included statistician's review of Protocol, previously submitted 7/17/92. First Phase 3 study conducted in the US under this IND. Provided responses to the FDA's questions, comments and recommendations concerning Protocol as delineated in the 5/3/93 communication.	IND Other-Letter/Form/Index	9/17/93
IND Safety Report: Initial Written Report.	IND Other-Letter/Form/Index	9/30/93
Petitioned Division of Metabolism and Endocrine Drug Products for uniform approval criteria for obesity therapies.	IND Other-Letter/Form/Index	10/8/93
IND Safety Report: Initial Written Report.	IND Other-Letter/Form/Index	10/15/93

Communication	Type of Communication	Date of Communication
IND Safety Report: Initial Written Report - Investigator.	IND Other-Letter/Form/Index	10/20/93
Protocol Amendment: New Investigators. Additional Investigator Information.	IND Amendment-Letter/Form/Index	11/8/93
Information Amendment: Chemistry, Manufacturing and Controls Information - Revised specifications and directions for testing.	IND Amendment-Letter/Form/Index	11/16/93
FDA comments/requests regarding a 2-year Phase III study and a drug interaction study with beta-carotene. Also requested additional drug interaction studies on usual therapies administered to obese populations.	FDA Letter	11/23/93
Protocol Amendment: New Protocol.	IND Amendment-Letter/Form/Index	12/7/93
IND Safety Report: Initial Written Report.	IND Other-Letter/Form/Index	1/18/94
Protocol Amendment: New Protocol - New Investigator. Information Amendment: Chemistry, Manufacturing and Controls.	IND Amendment-Letter/Form/Index	1/20/94
IND Safety Report: Initial Written Report.	IND Other-Letter/Form/Index	1/26/94
Protocol Amendment: Change in Protocols. New Investigators. Additional Investigator Information. Information Amendment: Chemistry, Manufacturing and Controls.	IND Amendment-Letter/Form/Index	1/31/94
IND Safety Report: Initial Written Report - Foreign ADE.	IND Other-Letter/Form/Index	2/16/94
Protocol Amendment: New Protocol - New Investigator.	IND Amendment-Letter/Form/Index	2/23/94
IND Safety Report: Initial Written Report - Foreign ADE.	IND Other-Letter/Form/Index	2/25/94
IND Safety Report: Initial Written Report.	IND Other-Letter/Form/Index	3/11/94
Response to FDA Request for Additional Information: Provided additional information requested in FDA letter dated 11/23/93, regarding two clinical studies, a two year Phase III study, and a Phase I interaction study.	IND Other-Letter/Form/Index	3/14/94
Telephone call 3/23/94 from FDA concerning Roche's 3/14/94 response to FDA letter dated 11/23/93.	File Note	3/25/94
Protocol Amendment: New Investigators. Changes in Investigators' Data.	IND Amendment-Letter/Form/Index	4/14/94
IND Safety Report: Initial Written Report.	IND Other-Letter/Form/Index	5/6/94
Information Amendment: Clinical.	IND Amendment-Letter/Form/Index	5/20/94
IND Safety Report: Initial Written Report.	IND Other-Letter/Form/Index	6/16/94
Information Amendment: Clinical - Final Study Reports.	IND Amendment-Letter/Form/Index	6/30/94
Annual Report covering the reporting period of 5/93 thru 5/94.	IND Annual Report-Letter/Form/Index	7/12/94
Protocol Amendment: New Protocol -New Investigator.	IND Amendment-Letter/Form/Index	7/25/94
IND Safety Report: Initial Written Report.	IND Other-Letter/Form/Index	8/10/94
Protocol Amendment: New Protocol - New Investigator.	IND Amendment-Letter/Form/Index	8/15/94
Information Amendment: Clinical - Final Study Reports.	IND Amendment-Letter/Form/Index	8/17/94

Communication	Type of Communication	Date of Communication
Information Amendment: Pharmacology/Toxicology - Two reports which are integrated summaries of the preclinical pharmacology data, clinical and preclinical ADME data to date. Requested an End-of-Phase 2 meeting with preclinical reviewers to discuss the overall preclinical research development program.	IND Amendment-Letter/Form/Index	8/30/94
Protocol Amendment: New Protocol - New Investigator.	IND Amendment-Letter/Form/Index	10/6/94
Information Amendment: Chemistry, Manufacturing and Controls.	IND Amendment-Letter/Form/Index	10/10/94
Information Amendment: Pharmacology/Toxicology - Provided copies of references.	IND Amendment-Letter/Form/Index	11/3/94
Protocol Amendment: New Protocol - New Investigator. Change in Protocol - New Investigator - Protocol.	IND Amendment-Letter/Form/Index	11/11/94
Meeting Request: Requested a pre-NDA meeting with preclinical reviewers to discuss the preclinical development plan.	IND Other-Letter/Form/Index	11/15/94
Information Amendment: Toxicology - Submitted a copy of the protocol for the repeat of the one year dog study.	IND Amendment-Letter/Form/Index	11/22/94
Desk Copies of Previously Sumitted Documentation - Provided desk copies of previous submissions to IND. These submissions include Serial Submissions 111 and 116 dated 8/30/94 and 11/15/94, respectively and address the requested meeting with the preclinical reviewers of this IND.	IND Other-Letter/Form/Index	1/5/95
Protocol Amendment: New Protocol - New Investigator. Information Amendment: Chemistry, Manufacturing and Controls - Drug Substance and Dosage Form.	IND Amendment-Letter/Form/Index	1/5/95
Discussion with FDA 1/9/95 regarding questions concerning the repeat one-year dog study with orlistat.	File Note	1/24/95
Provided copies of overheads to be presented by Roche representatives for meeting with preclinical reviewers scheduled for 1/31/95.	IND Other-Letter/Form/Index	1/26/95
Telephone call to FDA 2/14/95 to discuss female mice in the ongoing oncogenicity study For orlistat. On 2/15/95 FDA agreed to early termination of the study.	File Note	2/17/95
FAX - FDA minutes of the End of Phase II/pre-NDA held on 1/31/95 to discuss the progress of the Orlistat IND.	FDA Letter	2/23/95
Minutes of meeting with preclinical FDA Reviewers held on 1/31/95 to discuss the acceptability and completeness of orlistat's preclinical development research program for the NDA.	File Note	2/24/95
Meeting Request: Requested a meeting with FDA to discuss issues related to producing orlistat via fermentation rather than by chemical synthesis.	IND Other-Letter/Form/Index	3/13/95
Discussion with FDA concerning mouse carcinogenicity study.	File Note	5/22/95

Communication	Type of Communication	Date of Communication
Protocol Amendment: New Protocol - New Investigator.	IND Amendment-Letter/Form/Index	6/26/95
Annual Report	IND Annual Report-Letter/Form/Index	7/12/95
Information Amendment: Chemistry and Meeting Minutes: Minutes of teleconferences held 4/95 and 6/95, and discussions with FDA concerning fermentation as an alternative method of manufacture.	IND Amendment-Letter/Form/Index	7/17/95
Meeting with FDA held 1/31/95 to review overall preclinical program for Xenical.	IND Other-Letter/Form/Index	7/21/95
Protocol Amendment: New Protocol - New Investigator: Protocol.	IND Amendment-Letter/Form/Index	9/15/95
Response to FDA request regarding submission of draft protocols relative to the rat study for review and comment prior to initiation. At the 1/31/95 meeting FDA requested a chronic study in dogs. Submission dated 7/21/95, included Roche's plan of action to address colonic proliferation.	IND Other-Letter/Form/Index	9/19/95
Response to FDA Request for Information: During End-of-Phase 2 meeting held 4/30/92, discussed Orlistat clinical pharmacology and pharmacokinetics programs. FDA requested that protocols for bioequivalency testing be submitted for review and comment for future studies. Provided draft protocol designed to assess the equivalence between the dosage forms used during Phase 3 clinical trials and the to-be-marketed dosage forms following scaleup.	IND Other-Letter/Form/Index	10/4/95
Protocol Amendment: New Protocol - New Investigator: Protocol.	IND Amendment-Letter/Form/Index	11/3/95
FDA questions and comments concerning clinical and pharmacology regarding submission dated 7/21/95.	FDA Letter	11/8/95
Information Amendment: Chemistry, Manufacturing and Controls data for the Xenical dosage forms to be used during conduct of Protocol.	IND Amendment-Letter/Form/Index	11/8/95
Protocol Amendment: New Protocol. Response to FDA Request for Information in letter dated 11/8/95. Provided additional clinical and preclinical information.	IND Amendment-Letter/Form/Index	12/14/95
Comments on Clinical Pharmacology Protocol Addressing Colonic Proliferation	File Note	12/21/95
Protocol Amendment - New Protocol and New Investigator. Information Amendment.	IND Amendment-Letter/Form/Index	1/12/96
Protocol Amendment - Change in Protocol: Protocol, New Investigator.	IND Amendment-Letter/Form/Index	2/13/96
Request for pre-NDA CMC meeting to familiarize FDA personnel with CMC information and scientific rationale for the Original NDA for Xenical(orlistat) Capsules.	IND Other-Letter/Form/Index	6/18/96
Information Amendment: Pharmacology/Toxicology - Toxicology Final Study Reports.	IND Amendment-Letter/Form/Index	6/24/96

Communication	Type of Communication	Date of Communication
Request for Pre-NDA meeting with Biopharmaceutical reviewers to discuss issues related to the human pharmacokinetic section (Section 6) of the future NDA for Xenical.	IND Other-Letter/Form/Index	7/9/96
Provided pre-meeting documents for the meeting with Biopharmaceutical requested in submission dated 7/9/96, S-135.	IND Other-Letter/Form/Index	8/8/96
Information Amendment: Chemistry, Manufacturing and Controls - Overview of proposed NDA CMC Information and scientific rationale for the Original NDA for Xenical (orlistat) Capsules.	IND Amendment-Letter/Form/Index	9/3/96
Request for Priority Review designation for the future Xenical NDA and to request a meeting with FDA, to discuss priority review designation and potential logistics of completing a priority review within the user fee schedule.	IND Amendment-Letter/Form/Index	9/6/96
FAX - Minutes of meeting held on 9/18/96 with FDA regarding Pre-NDA CMC (teleconference).	FDA Letter	11/5/96
Response to FDA Request for Information. Provided Manufacturing site information for orlistat drug substance and dosage form, and the names and addresses of the clinical investigators.	IND Amendment-Letter/Form/Index	11/8/96
Protocol Amendment: New Protocol/New Investigator - Information Amendment: Chemistry/Microbiology	IND Amendment-Letter/Form/Index	2/10/97
Protocol Amendment: New Protocol/New Investigators. CRO Responsibilities: Addition of Safety Monitors. Information Amendment: Chemistry, Manufacturing and Controls (active and placebo) to be used in the initial Phase 3b study, Protocol.	IND Amendment-Letter/Form/Index	5/22/97
Annual Report covering the reporting period of 5/13/96 thru 5/12/97.	IND Annual Report-Letter/Form/Index	7/15/97
Other: Information regarding Swedish Study - Submission made to NDA 20-766 dated 8/27/97, included the Protocol which is being conducted in Sweden.	IND Other-Letter/Form/Index	9/25/97
Request for Pre-NDA Meeting to Discuss Resubmission of NDA 20-766 - Refer to Roche letter indicating withdrawal of NDA 20-766 on 8/27/97 without prejudice to refiling and to previous discussions with FDA on 8/26/97 concerning our intent to refile this application. Requested a meeting in October with FDA.	IND Other-Letter/Form/Index	9/30/97
Protocol Amendment: New Protocol.	IND Amendment-Letter/Form/Index	6/1/98
Protocol Amendment: New Protocols.	IND Amendment-Letter/Form/Index	7/1/98
Information Amendment: Pharmacology/Toxicology - Research Report.	IND Amendment-Letter/Form/Index	7/10/98
Information Amendment: Clinical - Final Study Report, Research Report, Final Study Report, Research Report, Final Study Report, Research Report.	IND Amendment-Letter/Form/Index	7/16/98

Communication	Type of Communication	Date of Communication
IND Safety IND Safety Report: Initial Written Report - Provided two safety reports for events occurring in non-US studies, which are part of the Phase 3b program being conducted in Europe.	IND Other-Letter/Form/Index	7/17/98
General Correspondence - Notified FDA of our decision to withdraw Serial Submission No. 146 dated July 1, 1998.	IND Other-Letter/Form/Index	7/29/98
Annual Report covering the period of July 1997 through July 1998.	IND Annual Report-Letter/Form/Index	8/3/98
Information Amendment: CMC - The amendment provides for revisions to the drug substance test specifications and directions for testing from those most recently submitted in the 1/12/97 Information Amendment (Submission Serial No. 131).	IND Amendment-Letter/Form/Index	8/19/98
Protocol Amendment: New Protocols.	IND Amendment-Letter/Form/Index	8/20/98
IND Safety Report: Follow-up to a Written Report (Serial No. 149) for an event occurring in a non-US study, which is part of the Phase 3b program being conducted in Europe.	IND Other-Letter/Form/Index	9/1/98
Protocol Amendment: New Investigators.	IND Amendment-Letter/Form/Index	9/2/98
FAX - FDA request for information regarding submission dated 8/20/98 (S-153), Study 46.	FDA Letter	9/4/98
Protocol Amendment: New Investigators.	IND Amendment-Letter/Form/Index	9/29/98
Protocol Amendment: Change in Protocol, and Information Amendment: CMC, also Addition of Study Safety Monitors and Identification of CRO Responsibilities.	IND Amendment-Letter/Form/Index	10/7/98
IND Safety Report: Initial Written Report and Follow-up to a Written Report - For a non-US IND Study. (non-US IND Study), ADE: Pseudolymphoma.	IND Other-Letter/Form/Index	10/9/98
IND Safety Report: Initial Written Report and Follow-up to a Written Report - For a non-US IND Study. Pt. RF, Protocol No. Unknown (non-US IND Study), ADE.	IND Other-Letter/Form/Index	10/16/98
Request from FDA for Additional Investigator Information. As requested by FDA on 9/28/98, we are providing the names and addresses of the investigators participating in the Phase 3b program for the purposes of an FDA audit of these sites.	IND Other-Letter/Form/Index	10/19/98
Request from FDA for Additional Information Regarding Our Phase 3b Program.	IND Other-Letter/Form/Index	11/6/98
IND Safety Report: Initial Written Report - For a Non-US IND Study.	IND Other-Letter/Form/Index	11/6/98
IND Safety Report: Initial Written Report - For a Non-US IND Study.	IND Other-Letter/Form/Index	11/9/98
IND Safety Report: Initial Written Report - For a Non-US IND Study.	IND Other-Letter/Form/Index	11/10/98
Protocol Amendment: New Investigators.	IND Amendment-Letter/Form/Index	11/17/98
IND Safety Report: Follow-up to a Written Report - Non-US IND Study.	IND Other-Letter/Form/Index	11/20/98
IND Safety Report: Follow-up to a Written Report - Non-US IND Study.	IND Other-Letter/Form/Index	11/20/98

Communication	Type of Communication	Date of Communication
IND Safety Report: Followup to a Written Report Non-US IND Study - Second Follow-up Safety Report - Submitted a completed MedWatch Form.	IND Other-Letter/Form/Index	11/24/98
IND Safety Report: Initial Written Report - For a Non-US IND Study.	IND Other-Letter/Form/Index	11/25/98
IND Safety Report: 7-day call-in (From a Non-US Source).	IND Other-Letter/Form/Index	12/2/98
IND Safety Report: Initial Written Report - For a Non-US IND Study.	IND Other-Letter/Form/Index	12/2/98
IND Safety Report: Initial Written Report (Non-US IND Study).	IND Other-Letter/Form/Index	12/3/98
IND Safety Report: Initial Written Report (Non-US IND Study).	IND Other-Letter/Form/Index	12/4/98
IND Safety Report: Initial Written Report (Non-US IND Study).	IND Other-Letter/Form/Index	12/4/98
Protocol Amendment: Change in Protocols. CV for Medical monitor.	IND Amendment-Letter/Form/Index	12/8/98
IND Safety Report: Follow-up to a Written Report (Non-US IND Study) - Initial written report was submitted on 12/2/98 (S-169). Submitted a completed MedWatch Form for the follow-up report.	IND Other-Letter/Form/Index	12/8/98
IND Safety Report: Follow-up to a Written Report - For a non-US IND Study, ADE: recurrence pancreatitis.	IND Other-Letter/Form/Index	12/9/98
IND Safety Report: Follow-up to a Written Report - For a non-US IND Study.	IND Other-Letter/Form/Index	12/14/98
IND Safety Report: Initial Written Report - (Non-US IND Event).	IND Other-Letter/Form/Index	12/16/98
IND Safety Report: Follow-up to a Written Report - (Non-US IND Study) - Initial written report was submitted to the IND on 12/2/98 (S-169) and a follow-up report was submitted to the IND on 12/8/98 (S-174). Provided a completed MedWatch form for the follow-up report.	IND Other-Letter/Form/Index	12/22/98
IND Safety Report: Initial Written Report.	IND Other-Letter/Form/Index	12/22/98
IND Safety Report: Follow-up to a Written Report - For a Non-US IND Event.	IND Other-Letter/Form/Index	1/5/99
IND Safety Report: Initial Written Report - For a Non-US IND Event.	IND Other-Letter/Form/Index	1/5/99
IND Safety Report: Initial Written Report - For a Non-US IND Event.	IND Other-Letter/Form/Index	1/5/99
IND Safety Report: Follow-up to a Written Report - (Non-US IND Event). Initial Written Safety Report and 1st Follow-up Report were submitted on 10/16/98 (S-159). Additional Follow-up Reports were submitted on 11/20/98 (S-165) and 12/9/98 (S-170). Provided a completed MedWatch form for the 6th Follow-up Report.	IND Other-Letter/Form/Index	1/6/99
IND Safety Report: Initial Written Report - 7-Day Call-In (Non-US Source) - Provided a MedWatch Form for an event that occurred in the United Kingdom.	IND Other-Letter/Form/Index	1/13/99
IND Safety Report: Initial Written Report (From a Non-US Source).	IND Other-Letter/Form/Index	1/25/99

Communication	Type of Communication	Date of Communication
IND Safety Report: Initial Written Report (Non-US Source) - Provided additional information and clarification of an event that occurred outside the United States which was previously reported in a 7-day call to FDA on 1/13/99 (S-185).	IND Other-Letter/Form/Index	1/25/99
IND Safety Report: Initial Written Report (Non-US Source) - Provided an Analysis of Similar events, as well as a completed MedWatch Form for the Initial Written Report.	IND Other-Letter/Form/Index	1/25/99
IND Safety Report: Initial Written Report (Non-US Source) - Provided an Analysis of Similar Events, as well as a completed MedWatch Form for the Initial Written Report.	IND Other-Letter/Form/Index	1/29/99
IND Safety Report: Follow-up to a Written Report (Non-US IND Study)--Third follow-up report. Provided a completed MedWatch Form for this follow-up report. The Initial Written Report was submitted on 11/6/98 (S-161). Additional follow-up reports were submitted 11/20/98 (S-166) and 11/24/98 (S-167).	IND Other-Letter/Form/Index	2/1/99
IND Safety Report: Follow-up to a Written Report (Non-US IND Event) - Provided a completed MedWatch Form for this follow-up report. The Initial Written Report was submitted to the IND on 12/22/98 (S-179).	IND Other-Letter/Form/Index	2/1/99
IND Safety Report: Initial Written Report (From a Non-US Source).	IND Other-Letter/Form/Index	2/8/99
IND Safety Report: Initial Written Report (Non-US Source).	IND Other-Letter/Form/Index	2/17/99
IND Safety Report: Follow-Up to a Written Report (Non-US Source) - Provided a completed MedWatch Form for this follow-up report. The Initial Written Report was submitted on 1/25/99 (S-186).	IND Other-Letter/Form/Index	2/18/99
Protocol Amendment: New Investigators.	IND Amendment-Letter/Form/Index	2/19/99
IND Safety Report: Initial Written Report (From a Non-US Source).	IND Other-Letter/Form/Index	2/25/99
IND Safety Report: Initial Written Report (From a Non-US Source).	IND Other-Letter/Form/Index	2/25/99
IND Safety Report: Follow-Up Report - For a Non-US IND Event.	IND Other-Letter/Form/Index	2/26/99
IND Safety Report: Initial Written Report (From a Non-US Source).	IND Other-Letter/Form/Index	2/26/99
IND Safety Report: Follow-Up Report(From a Non-US Source).	IND Other-Letter/Form/Index	3/11/99
IND Safety Report: Follow-Up Report (From a Non-US Source).	IND Other-Letter/Form/Index	3/11/99
IND Safety Report: Initial Written Report (Non-US Source).	IND Other-Letter/Form/Index	3/15/99
Protocol Amendment: Change in Protocol originally submitted to the IND on 8/20/98 and subsequently amended on 10/7/98.	IND Amendment-Letter/Form/Index	3/16/99
IND Safety Report: Initial Written Report (From a Non-US Source).	IND Other-Letter/Form/Index	3/18/99
IND Safety Report: Initial Written Report (From a Non-US Source).	IND Other-Letter/Form/Index	3/18/99
IND Safety Report: Initial Written Report (Non-US Source) - Submitted an Analysis of Similar events, as well as a completed MedWatch Form for the Initial Written Report.	IND Other-Letter/Form/Index	3/24/99

Communication	Type of Communication	Date of Communication
IND Safety Report: Initial Written Report (Non-US Source).	IND Other-Letter/Form/Index	3/25/99
IND Safety Report: Follow-up to a Written Report (Non-US Source) - Submitted a completed MedWatch Form for this follow-up report. The Initial Written Report was submitted on 12/16/98.	IND Other-Letter/Form/Index	3/29/99
IND Safety Report: Initial Written Report (Non-US Source) - Submitted an Analysis of Similar Events as well as a completed MedWatch Form for the Initial Written Report.	IND Other-Letter/Form/Index	3/29/99
IND Safety Report: Follow-up Report (From a Non-US Source).	IND Other-Letter/Form/Index	4/6/99
IND Safety Report: Follow-Up Report (From a Non-US Source).	IND Other-Letter/Form/Index	4/6/99
IND Safety Report: Second Follow-up Report - Non-US IND Study - Submitted a completed MedWatch Form for this follow-up report. The Initial Written Report was submitted on 11/9/98 and the first follow-up report was submitted on 11/25/98.	IND Other-Letter/Form/Index	4/8/99
IND Safety Report - FAX	IND Other-Letter/Form/Index	4/8/99
IND Safety Report: Third Follow-up to a Written Report - Non-US IND Study - Initial Safety Report was previously submitted on 7/17/98. Follow-up reports were previously submitted on 9/1/98 and 12/14/98. Submitted a completed MedWatch Form for this third follow-up report.	IND Other-Letter/Form/Index	4/8/99
IND Safety Report: Initial Written Report (Non-US Source)	IND Other-Letter/Form/Index	4/15/99
IND Safety Report - FAX Sent to FDA providing information regarding an IND Safety Report.	IND Other-Letter/Form/Index	4/21/99
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Xenical NDA
20-766

Communication	Communication type	Date of Communication
Xenical Capsules for long-term weight control (weight loss, weight maintenance and prevention of weight regain) in conjunction with a mildly hypocaloric diet.	NDA Original	11/26/96
FDA acknowledged receipt of Original NDA for Xenical Capsules submitted 11/26/96, for long-term weight control in conjunction with a mildly hypocaloric diet.	FDA Letter	12/2/96
Provided on loan the equipment and software for the Xenical CANDA to facilitate the review of our application for Xenical. The CANDA will be delivered to FDA on the morning of 12/20/96.	NDA Other	12/17/96
FAX - FDA requests regarding Chemistry, Statistical and Clinical. These requests were made during the teleconference on 1/7/97.	FDA Letter	1/9/97
Provided additional statistical analyses requested in FDA fax dated 1/9/97 prior to filing of this NDA. Requested priority review for NDA 20-766.	NDA Amendment	1/15/97
FAX - FDA provided the format for submission of the statistical portion of animal carcinogenicity data for Xenical NDA.	FDA Letter	1/21/97
Response to FDA telefax of 1/9/97 concerning the CMC information included in the Xenical NDA.	NDA Amendment	1/22/97
Provided FDA with an additional copy of Volume 1 of NDA 20-766 including overall index.	NDA Amendment	1/24/97
Response to FDA's fax of 1/21/97 requesting the statistical portion of animal carcinogenicity in electronic format.	NDA Amendment	1/28/97
As agreed at the 1/7/97 teleconference, we are providing additional statistical analyses after the filing of NDA 20-766.	NDA Amendment	1/28/97
Response to FDA's (Pharmacokinetic Review) request for Human Pharmacokinetic Summary.	NDA Amendment	1/28/97
Delivery of CD-ROM containing SAS datasets requested by statistical reviewers. Additional vitamin data is also included on the CD-ROM, requested by FDA (statistical reviewer) on behalf of the medical reviewer during a teleconference on 1/23/97.	NDA Amendment	1/28/97
Delivery of Equipment: Backup solution to the Micropolis Drive. Provided on loan equipment for the use of FDA, Statistician, to assist in the review of SAS datasets.	NDA Amendment	1/29/97
Teleconference 1/29/97 between FDA, Division of Investigation, and Hoffmann-La Roche. FDA requested: 1. Protocols. 2. List of principal investigators and number of patients each investigator studied.	File Note	1/29/97
Provided additional biopharmaceutical data as requested by FDA on 1/29/97.	NDA Amendment	1/29/97
Delivery of Equipment - Provided on loan equipment for the use of FDA, Statistician, to assist in the review of SAS datasets. The equipment will be delivered on 1/30/97.	NDA Amendment	1/29/97
Response to FDA Request for clinical information discussed during teleconference on 1/29/97.	NDA Amendment	1/29/97
FAX - FDA request for information to facilitate completion of the medical review.	FDA Letter	1/29/97

Communication	Communication type	Date of Communication
Response to FDA Request for additional Statistical Information. Provided a memorandum regarding clarification of medical review questions and a brief summary of notes from a meeting on 1/30/97.	NDA Amendment	1/31/97
Amendment to CMC section of pending Xenical NDA. Amendment provides physical evidence to demonstrate that the key intermediate has the correct absolute configuration as described in the Original NDA submission of 11/26/96.	NDA Amendment	2/3/97
Submitted a field copy of the cover letter, completed Form FDA 3439 and the attachment for the referenced NDA.	NDA Field/Desk Copy	2/3/97
Informed FDA that Roche has no objections to interactions between FDA and the Health Protection Branch concerning the review of NDA 20-766 for Xenical.	NDA Amendment	2/4/97
In response to FDA's request, Roche provided an Assay Validation Document for the Determination of Plasma B-Carotene and Serum Vitamins A and E.	NDA Amendment	2/4/97
Response to FDA Fax of 1/29/97 in which FDA requested additional information on the Vitamins and Beta-Carotene, and the Integrated Summaries of Efficacy and Safety.	NDA Amendment	2/5/97
Response to FDA request for additional biopharmaceutical information. Provided batch sizes and certificates of analysis.	NDA Amendment	2/5/97
Response to FDA Request for Information included in fax dated 1/29/97, requesting additional information on the Vitamins and Beta-Carotene Study and the Integrated Summaries of Efficacy and Safety to be provided for NDA 20-766. Provided answers to questions and additional information.	NDA Amendment	2/10/97
Response to FDA request for additional Biopharmaceutical Information. Provided the certificates of analysis for certain lots.	NDA Amendment	2/10/97
Response to FDA Request for References. Provided either copies of, or the location in NDA 20-766, for the nine references cited.	NDA Amendment	2/11/97
Response to Biopharmaceutical Reviewer's Request for Information. Provided additional information concerning the data included in Section 6 of the NDA.	NDA Amendment	2/11/97
Response to FDA Request for electronic copy of labeling. Provided six computer disks, each containing a copy of the proposed labeling for Xenical Capsules. The labeling is provided in two different formats.	NDA Other	2/12/97
As requested by FDA on 2/2/97, Roche provided additional clinical information.	NDA Amendment	2/13/97
Response to FDA request for additional biopharmaceutical information requested on 2/18/97. Provided clarification of the batches used to set the specifications.	NDA Amendment	2/18/97

Communication	Communication type	Date of Communication
Telephone conversation with FDA regarding batches used to set the dissolution specification and selection of the dissolution medium	File Note	2/21/97
Response to FDA request for additional subanalyses for weight loss and risk factors made on 2/21/97.	NDA Amendment	2/24/97
As requested, Roche provided a disk with the synopsis for Protocol included in Section 6 of the NDA. A paper copy was also provided.	NDA Other	2/26/97
Response to FDA's, Statistical Reviewer, request provided nine diskettes containing the lipid data sets for the following six Phase 3 studies.	NDA Other	3/4/97
In response to FDA's request on 2/18/97, Roche provided additional information concerning the rationale for the use of 3% Sodium Lauryl Sulfate in the dissolution medium.	NDA Other	3/5/97
In response to FDA's request, provided some of the data requested for patients with DEXA measurements conducted during the Phase 3 clinical program for orlistat at two study sties, and provided the information requested with respect to the number of patients who required doubling of their vitamin supplementation during the first and second year of treatment and the statistical differences from placebo.	NDA Other	3/24/97
FAX - FDA request for information regarding CMC and Biopharmaceutics sections of the NDA. Also provided comments and recommendations for the labeling.	FDA Letter	3/27/97
FDA request for information regarding CMC and Biopharmaceutics sections of the NDA. Also provided comments and recommendations for the labeling.	FDA Letter	3/27/97
Request for confirmation of waiver of Roche Basel site inspection as indicated by FDA International Office on 4/7/97 as a requirement for approval of Xenical Capsules.	NDA Other	4/9/97
Four-Month Safety Update - The Phase 3 studies were completed, and the data for all patients was previously provided in NDA 20-766. Errata identified in the database as of 3/31/97 are provided in this safety report.	NDA Other	4/9/97
FDA Response to Request for Confirmation of Waiver of Basel Inspection	File Note	4/15/97
Briefing document for the 5/14/97 meeting of the Endocrinologic and Metabolic Advisory Committee.	NDA Other	4/22/97
FAX - Additional labeling comments in addition to comments faxed on 3/27/97.	FDA Letter	4/28/97
Filed copy of CMC Amendment responding to FDA letter of 3/27/97, requesting additional information regarding the chemistry section.	NDA Other	4/28/97
Amendment - Chemistry, Manufacturing and Controls - Response to FDA letter of 3/27/97 requesting additional information regarding the chemistry section.	NDA Amendment	4/28/97

Communication	Communication type	Date of Communication
Response to FDA Request for Additional Information on DEXA measurements. Data for study site was provided in a submission dated 3/24/97. This submission provides both the bone metabolism and DEXA data.	NDA Other	4/29/97
FAX - Additional comments pertaining to the Pharmacology section, in addition to comments faxed on 4/28/97.	FDA Letter	4/29/97
FAX from FDA with questions regarding Xenical for the May 14, 1997 Advisory Committee Meeting.	FDA Letter	5/1/97
Endocrinologic and Metabolic Advisory Committee Meeting--5/14/97. Roche opposition to release of confidential information to a third party and opposition to any modification of the previously published meeting agenda.	NDA Other	5/8/97
FDA documentation for Endocrinologic and Metabolic Drugs Advisory Committee Meeting to be held 5/14/97 regarding Xenical.	FDA Letter	5/14/97
Promotional material:Dear Doctor letter which discusses the FDA's Advisory Committee's recommendation for approval of Xenical	NDA Other	5/15/97
Additional information as requested for patients as discussed on 5/16/97 and 5/19/97.	NDA Amendment	5/23/97
FAX - FDA acknowledged receipt of our 5/23/97 amendment providing information requested on 5/16/97 and 5/19/97. FDA considers this a major amendment received within three months of user fee due date, therefore, the user fee clock is extended to 8/27/97.	FDA Letter	5/27/97
Response to FDA Request for Supporting Documentation for Quality of Life development section of the NDA and for validation study supporting these data. Provided copies of cited references.	NDA Other	6/3/97
Response to FDA Request for Comments on Draft Labeling - Three FDA faxes dated 3/27/97, 4/28/97 and 4/29/97 included labeling recommendations from the following reviewers: chemistry, biopharmaceutics, pharmacology and medical.	NDA Amendment	6/3/97
FDA discusses "Dear Doctor" letter dated 5/15/97, regarding Advisory Committee's recommendation for approval of Xenical.	FDA Letter	6/6/97
Response to FDA Request for Electronic Copy of Draft Labeling - Provided two computer disks, each containing a copy of the proposed draft labeling for Xenical Capsules.	NDA Other	6/10/97
Response to FDA Request for Additional Version of Labeling on Disk - Provided an edited version electronically.	NDA Other	6/13/97
Response to FDA Request for Additional Version of Labeling on Disk - Provided an edited version of the 6/2 draft labeling.	NDA Other	6/16/97

Communication	Communication type	Date of Communication
Response to FDA letter dated 6/6/97 concerning Hoffmann-La Roche's letter dated 5/15/97 discussing the Metabolic and Endocrinologic Advisory Committee review of NDA 20-766 for Xenical.	NDA Other	6/17/97
FAX - FDA provided background material for the teleconference scheduled for 7/1/97.	FDA Letter	6/27/97
FAX - FDA comments/changes regarding the Xenical label.	FDA Letter	6/27/97
FDA has reviewed our 6/17/97 response to their 6/6/97 letter. DDMAC notes that Roche has discontinued use of this material and finds the actions taken to be acceptable.	FDA Letter	6/30/97
In response to FDA's Fax of 6/27/97, Roche provided a response to the Agency's comments on the XENICAL labeling, including labeling changes suggested by the Division.	NDA Amendment	7/23/97
Provided an electronic copy of Roche's response to FDA's draft labeling of 6/27/97 and four additional copies of Volume 1.	NDA Other	7/24/97
Market Exclusivity Information which supplements exclusivity information provided with the NDA and is submitted for inclusion in this NDA.	NDA Other	7/30/97
Progress report on response to FDA request of 7/1/97. Roche provided a description of the work the company is conducting to address questions raised on 7/1, and this work is currently being summarized for submission on 8/21.	NDA Other	8/15/97
Teleconference with FDA, Division Director and CSO on August 12, 1997	File Note	8/19/97
The 8/15/97 submission addressed the preliminary results of the followup survey being conducted in women greater than 45 years of age who participated in the Phase 3 clinical trials.	File Note	8/20/97
FAX - FDA comments re. "coming soon" advertisement which appears in the 8/97 issue of Journal of American Dietetic Assn.	FDA Letter	8/21/97
Response to FDA Request of 7/1/97 - Provided information not included in a previous submission also dated 8/21/97.	NDA Other	8/21/97
Summary from FDA Teleconference with FDA, CSO to discuss NDA 20-766 on August 20, 1997	File Note	8/22/97
FDA withdrawal of Xenical Capsules NDA in compliance with our request dated 8/27/97. Application is withdrawn as of 8/27/97.	FDA Letter	8/27/97
Response to FDA Request to review Swedish Study and questions concerning Swedish Health Care System. Provided Swedish Study protocol for FDA review and comment.	NDA Other	8/27/97
Withdrawal of Unapproved Application - Notified FDA of withdrawal of Xenical NDA.	NDA Other	8/27/97
Response to FDA letter dated 8/21/97 concerning a Roche "coming soon" advertisement appearing in the 8/97 issue of The Journal of the American Dietetic Association.	NDA Other	9/3/97

Communication	Communication type	Date of Communication
FAX - FDA acknowledged receipt of our 9/3/97 letter responding to their 8/21/97 letter and finds our decision to discontinue this advertisement acceptable.	FDA Letter	9/19/97
FDA Meeting on August 26, 1997	File Note	9/23/97
FDA Meeting on August 25, 1997	File Note	9/23/97
FDA Teleconference	File Note	9/23/97
FDA Teleconference on August 26, 1997	File Note	9/23/97
FDA comments on their review of the protocol submitted 8/27/97.	FDA Letter	10/2/97
FDA response to our 9/30/97 request for a meeting to discuss issues related to resubmission of Xenical.	FDA Letter	10/10/97
FAX -FDA response to our 9/30/97 request for a meeting to discuss issues related to the resubmission of Xenical NDA.	FDA Letter	10/10/97
FAX - FDA provided two sets of meeting minutes: 8/25/97 Meeting: (to obtain assessment of the 8/21/97 submission), and 8/26/97 Meeting (to discuss Roche option of withdrawing NDA for Xenical).	FDA Letter	11/5/97
Resubmission of NDA 20-766 - Application provides additional information. Resubmission consists of 22 additional volumes for Section 8/10 only (Volumes 672 through 694). As agreed during meeting of 8/26/97, it is Roche's understanding that this application will be granted priority review status.	NDA Amendment	11/14/97
FDA acknowledged receipt 11/17/97 of resubmitted Xenical NDA dated 11/14/97.	FDA Letter	11/19/97
Meeting agenda for 2/11/98 meeting to discuss the presentation of Xenical at the March 13, 1998 meeting of the Endocrinologic and Metabolic Drugs Advisory Committee.	NDA Other	1/30/98
FAX - FDA request for an update of the Swedish Study to be submitted by the third week of February.	FDA Letter	2/2/98
Response to FDA request for information on 1/23 and 1/26/98. We have provided information for seven Phase III clinical protocols.	NDA Other	2/4/98
Draft Labeling: Patient Insert and Professional Package Insert submitted for review and comment.	NDA Other	2/5/98
Submitted information requested by FDA, including in Table 2 a presentation of trial patient-years divided between patients receiving 30 and 60 mg of Xenical.	NDA Other	2/6/98
Response to FDA Request for Information - As requested at our meeting of 2/11/98, provided the following: - Summary of breast cancer risk factors collected via survey - Two expert reports.	NDA Other	2/12/98

Communication	Communication type	Date of Communication
Response to FDA Request for Information: We have submitted two copies of Volumes 14, 15 and 16, the Methods Validation for Xenical. These volumes were originally submitted in the 11/26/96 submission of NDA 20-766.	NDA Other	2/18/98
Request for Additional Information: As requested on 2/11/98 at our meeting to discuss issues related to the review of our NDA and upcoming Advisory Committee scheduled for 3/13/98, FDA requested any data or documentation not previously submitted which is intended to be included in the sponsor's briefing document. Roche provided some additional information requested.	NDA Other	2/18/98
Briefing Document for 3/13/98 Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee - Provided 30 copies for the meeting.	NDA Other	2/18/98
Response to FDA Request for Information: As requested on 2/13/98 Roche provided further information.	NDA Other	2/20/98
Response to FDA Request for Information - Provided information regarding status of the trial. At the meeting of 2/11/98 with the Division, we agreed to obtain input from outside experts as to whether the trial could provide definitive information. The final expert response will be available early the week of 2/22 and will be submitted to FDA at that time.	NDA Other	2/20/98
Response to FDA request for information on Trial - Follow-up to submission on 2/20/98.	NDA Other	3/3/98
Response to FDA Request for Information - Submitted the mean (+/-SD) and median, change and percent change from baseline in body weight over time for studies.	NDA Other	3/3/98
Response to FDA Request for Additional Statistical Information: As requested we have provided the modified previous analysis using two groups (P vs. 120) instead of three groups.	NDA Other	3/5/98
Informed FDA that Roche will submit labeling statements and an overview of its ongoing and planned phase IIIb and IV program.	File Note	3/5/98
Four-Month Safety Update - Submitted the Four-Month Safety Update for the re-submission of NDA 20-766 dated 11/14/97.	NDA Amendment	4/1/98
Proposed Post-Marketing Commitments - During teleconference of 3/31/98 between FDA and Roche, Roche proposed post-marketing surveillance commitments to be implemented following approval of this application. This submissions provides a more detailed presentation of this proposal and also includes responses to questions raised at the Advisory Committee on 3/13/98.	NDA Other	4/9/98
Review Status of FDA Approval of NDA for Xenical	File Note	4/15/98
Follow-up to Teleconference on 4/13/98 - Provided assurance to FDA that Roche has proposed a comprehensive program. In our submission dated 4/9/98, Roche proposed labeling.	NDA Other	4/16/98

Communication	Communication type	Date of Communication
Submission of estrogen data previously provided via Fax on 3/11/98, and additional estrogen data not previously submitted.	NDA Other	4/21/98
Discuss plans for NDA decision-making meeting with FDA.	File Note	4/22/98
Discuss upcoming meeting of May 7 and agreement on meeting format	File Note	5/6/98
Discuss FDA plan to issue an approvable letter and conditions for approval.	File Note	5/11/98
FDA issued approvable letter for NDA. Final approval is contingent upon submission and review of additional data.	FDA Letter	5/12/98
Discuss approvable letter to be issued by FDA on 5/12/98 and submission and review of additional data.	File Note	5/12/98
FDA request that Roche discontinue dissemination of a press release dated 5/13/98 which appeared on the Roche Internet web site. Written response should be submitted to DDMAC on or before 5/22/98.	FDA Letter	5/14/98
Response to Approvable Letter - As requested on 5/12/98 Roche notifyed FDA of intent to file an amendment.	NDA Other	5/15/98
FAX - FDA requested information for Studies.	FDA Letter	5/20/98
Response to FDA letter dated 5/14/98 concerning Hoffmann-La Roche's press release dated 5/13/98 appearing on the Internet web site.	NDA Other	5/22/98
Discuss information on patient from study.	File Note	5/22/98
Proposal for Aggregate Database and Request for Teleconference. Teleconference was held with FDA 5/11/98 to discuss various aspects of the Xenical NDA approval process and the aggregate database to be utilized to replicate the NDA database consisting of the four Phase 3a studies. Requested a teleconference to discuss the proposed aggregate database.	NDA Other	5/27/98
Additional Information Requested for Non-US Phase 3b Studies on 5/20/98.	NDA Other	7/6/98
FDA request for samples/information to perform method verification studies on Xenical Capsules in connection with NDA 20-766.	FDA Letter	7/8/98
Additional information requested for July 22, 1998 teleconference. Roche provided a response to the questions included in the July 15, 1998 fax.	NDA Other	7/17/98

Communication	Communication type	Date of Communication
Follow-up to Teleconference of 7/29/98 - During teleconferences on 7/23 and 7/29/98, informed FDA of Roche's response to comments from the Division of Metabolic and Endocrine Drug Products on two questions that were posed to the Division in May. This letter serves to summarize the sponsor's position regarding: Definition of the Size of the "NDA Database" and Conducting Clinical Trials in the US.	NDA Other	7/31/98
As agreed at our 7/22/98 teleconference we are submitting a proposal for the auditing of the Phase IIIb studies being conducted in Europe.	NDA Other	8/11/98
Discussed meeting with the FDA team responsible for reviewing the Xenical NDA.	File Note	8/18/98
Response to FDA's Request for Additional Information on Two Cases of Benign Breast Tumors as discussed in the July 22 teleconference.	NDA Other	9/9/98
Letter to: Northeast Regional Laboratory - Method Validation Samples - Response to request received on 7/8/98 for samples to be used for method validation verification studies on Xenical Capsules in connection with NDA 20-766. Provided a list of items provided in this package.	NDA Other	9/10/98
Letter to: FDA, St. Louis, Missouri - Method Validation Samples - Response to request received on 7/8/98 for samples to be used for method validation verification studies on Xenical Capsules in connection with NDA 20-766. Provided a list of items provided in this package.	NDA Other	9/10/98
FDA acknowledged receipt on 9/11/98 of sample materials for methods validation of NDA 20-766 submitted 9/10/98. Methods validation testing will be assigned as soon as scheduling permits.	FDA Letter	9/14/98
FDA requested additional information on the two cases and a general update on the status of outstanding issues such as new aggregate database proposal and Roche's audit proposal for Phase 3b studies.	File Note	9/18/98
FDA response to Roche submission dated 5/22/98, concerning the 5/14/98 Notice of Violation letter issued by DDMAC with regard to a 5/13/98 press release dated 5/13/98 appearing on the Roche Internet. Roche's revised version of the press release is acceptable.	FDA Letter	9/28/98
FDA has reviewed submission dated 8/11/98 which outlines a proposal for auditing sites of the European Phase 3b program. Requested information to plan and prepare for FDA audit.	FDA Letter	9/28/98
FAX -FDA response to Roche submission dated 5/22/98, concerning the 5/14/98 letter issued by DDMAC with regard to the 5/13/98 press release appearing on the Roche Internet. Roche's revised version of the press release is acceptable.	FDA Letter	9/28/98
FAX - FDA has reviewed submission dated 8/11/98 which outlines a proposal for auditing sites of the European Phase 3b program. Requested information to plan and prepare for FDA audit.	FDA Letter	9/28/98

Communication	Communication type	Date of Communication
Revised Proposal for Aggregate Data Set to Address Breast Cancer Observation in Phase 3a Studies- Approvable letter dated 5/12/98 states that final approval of this application is contingent on submission of additional data from an aggregate data set. In 12/98, the aggregate data set will be adequate to replicate Phase 3a NDA database.	NDA Other	10/7/98
Response to FDA Request for Information - FDA fax dated 9/3/98 requested Roche's rationale for not monitoring fat-soluble vitamin levels in the US Phase 3b studies. FDA also requested clarification on whether the two patients continued treatment with Xenical (see submission dated 9/9/98).	NDA Other	10/13/98
Export Notification - Notification to FDA that the following unapproved drug will be exported to and received by Switzerland (a listed country).	NDA Other	10/16/98
Response to FDA Request of September 28, 1998 - Identification of all Patients with a Breast Cancer Diagnosis. Informed FDA of intent to conduct an audit of the Phase 3b study sites and requested the identification of all patients with a breast cancer diagnosis.	NDA Other	10/30/98
FAX - FDA request for information/documentation to facilitate Xenical's approval. Division of Scientific Inspection to audit 8 centers in Sweden and Spain by 1/99.	FDA Letter	11/23/98
Information Request Response: We provided copies of the information previously requested by FDA on 11/23/98.	NDA Other	12/22/98
New Correspondence: Request for Waiver of Pre-Approval Reinspections.	NDA Other	1/6/99
Response to 5/12/98 Approvable Letter which states that final approval of this application is contingent upon submission and review of additional data.	NDA Other	1/18/99
Rationale and Supporting Documentation for Draft Labeling Previously Submitted 1/18/99-- Submission dated 1/18/99 was in response to FDA's approvable letter dated 5/12/98.	NDA Other	1/21/99
Amendment to Pending Original NDA submitted 11/26/96 - Chemistry, Manufacturing and Controls - The amendment includes a revised Master Production Batch Record. All other information remains unchanged from that submitted in the Original NDA and amendments thereto.	NDA Amendment	1/21/99
Discuss Submission in Response to Approvable Letter dated Jan. 18, 1999 Discuss Overall Review Process and Timelines	File Note	1/22/99
Response to FDA Request for Information - Provided the draft professional insert and the draft patient package insert on a diskette. A hard copy of this information was previously submitted on 1/21/99.	NDA Other	1/25/99

Communication	Communication type	Date of Communication
Response to FDA Request for Information - Provided another diskette that contains the draft professional package insert and the draft patient package insert.	NDA Other	1/27/99
FDA acknowledged receipt of our 1/18/99 submission, which was in response to FDA 's 5/12/98 action letter. The request for waiver of reinspection has been forwarded to the appropriate office for a decision.	FDA Letter	2/1/99
Discuss Overall Review Process and Possible Timelines Clarification of Information needed for Safety Update	File Note	2/3/99
Update of Information - Submission dated 1/18/99 was in response to the 5/12/98 approvable letter and included a report. A proposal for the aggregate data set was submitted 10/7/98 and accepted by FDA on 10/28/98. Roche agreed to provide monthly updates on this data.	NDA Other	3/2/99
Information Request Response: Safety Update for Post-Phase 3a Clinical Studies. As requested by FDA, we are providing the safety update including only serious adverse events and these events are categorized into two groups--control clinical trials or post-marketing experience.	NDA Other	3/11/99
FAX - FDA comments and recommended revisions to the physician package insert. Patient package insert has been revised and reformatted by DDMAC with concurrence from the Metabolic & Endocrine Division.	FDA Letter	3/17/99
Update of Breast Cancer Information - The 1/18/99 submission was in response to the 5/12/98 approvable letter and included a report entitled, "Integrated Summary of Breast Cancer Information." We are providing the second monthly update for the exposure and breast cancer information in the aggregate data set. This second update includes the exposure data as of 2/28/99 and breast cancer data as of 3/17/99.	NDA Other	3/22/99
Additional Information Requested for Non-US Phase 3b Studies on 5/20/98.	NDA Other	3/22/99
Professional and Patient Labeling - A teleconference was held 3/22/99 between FDA and Roche to discuss the labeling previously provided to Roche in a fax dated 3/17/99. During that teleconference, Roche agreed to send paper copies and electronic versions of the label to FDA as soon as possible. This submission contains copies of the label we agreed to.	NDA Other	3/23/99
Professional Labeling - Submitted a revised copy of the Professional Package Insert that is intended to replace the Professional Labeling previously submitted to the Agency on 3/23/99.	NDA Other	3/24/99

Communication	Communication type	Date of Communication
Information Request Response: Submitted statistical tables and professional labeling which include the weight loss and glycemic control data for diabetes study and agreement on including metabolic and cardiovascular risk factor data in text format in the label for the same study.	NDA Other	3/26/99
Draft Professional Labeling - As discussed in 3/22/99 teleconference, provided both paper copies and disc with the professional package insert with all the requested versions (accepted and annotated versions). This labeling supercedes all previous versions of the Xenical labeling and includes all corrections provided by the Review Division.	NDA Other	3/30/99
Professional and Patient Labeling - As discussed on 4/1/99, provided additional changes to the physician and patient labeling.	NDA Other	4/1/99
Container Label and ADA Guidelines for OGTT Status - Information Request Response: Provided additional information regarding questions discussed at our teleconference on 4/5/99.	NDA Other	4/5/99
Draft News Release, Media Q&A and Professional Labeling - Provided information to DDMAC discussing the review process for the draft press release announcing the approval of Xenical.	NDA Other	4/7/99
Draft News Release, Media Q&A and Professional Labeling - Conversation with DDMAC on 4/7/99 discussing review process for the draft press release announcing approval of Xenical.	NDA Other	4/7/99
Draft Launch Material - Provided to DDMAC draft launch materials for pre-approval prior to use.	NDA Other	4/8/99
Draft Launch Material - Provided to CSO draft launch materials for Xenical which are being submitted for pre-approval.	NDA Other	4/8/99
Revised Commitment for Monthly Updates of Exposure Data for Women/Press Release Announcing Approval - Provided a copy of the press release announcing approval of Xenical.	NDA Other	4/23/99
FAX - FDA approval of Xenical Capsules NDA submitted 11/26/96, which provides for use of Xenical for obesity management including weight loss and weight maintenance.	FDA Letter	4/23/99
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